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The Incidence of Haemolytic Disease of the Foetus ("Erythroblastosis Foetalis") in Different Families. The Value of Serological Tests in Diagnosis and Prognosis.

(A Report to the Medical Research Council from the S.W. London Blood Supply Depot.)

BY

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IT is now generally accepted that the disease Erythroblastosis Foetalis, better called Haemolytic Disease of the Foetus (or Newborn) is caused by the action on the foetal erythrocytes of immune agglutinins formed in the mother's serum during pregnancy and passed through the placenta into the foetal circulation. Levine and his coworkers (Levine and Stetson[1]; Levine *et al*[2]) first brought forward evidence to show that the formation of these agglutinins is stimulated by an antigen present in the foetal red cells but absent from the maternal red cells, the antigen having been inherited from the father, and they demonstrated that the Rh agglutinogen must be the antigen responsible in a very large proportion of the cases. For whereas the blood of only 15 per cent of subjects taken at random was found to be Rh negative (i.e. the erythrocytes lacked the Rh agglutinogen), among the mothers of infants affected with haemolytic disease, as many as 93 per cent were Rh negative, whereas all the infants and fathers tested were Rh positive. It was, therefore, concluded that the destruction of the foetal erythrocytes (Rh positive) was caused by the formation of anti-Rh agglutinins in the serum of the mother (Rh negative). Confirmatory observations have been published by Wiener[3] and by Boorman, Dodd and Mollison.[4]

A great deal more remains to be learnt about the whole process, however. For instance, although the combination Rh positive infant and Rh negative mother occurs in 9.46 per cent of all pregnancies (Haldane[5]), it seems clear that the infant is affected with haemolytic disease in only a small proportion of these cases for the incidence of haemolytic disease is only one in 400 or 0.25 per cent of all pregnancies. For this reason the mere demonstration that the mother is Rh negative and the infant Rh positive, cannot by itself be regarded as satisfactory diagnostic evidence of haemolytic disease of the foetus. Moreover, since the mother is Rh positive in a small proportion of cases in which the infant is affected with this disease, such a finding will not serve to exclude the diagnosis.

It is hoped that an analysis of the results obtained from serological tests made on a

large series of families may help in the assessment of the value of these tests in diagnosis and prognosis.

METHODS.

One hundred* families were tested because of the birth of a foetus suspected of being affected with haemolytic disease. In every case the mother was tested and in the majority of cases the infant or father was also examined. In many families one or more of the previous siblings were also tested. In another 70 cases tests were made on women who had given birth to one or more stillborn foetuses; and in a further 60 cases in which the infant was thought to be affected with "physiological jaundice" mother and infant were tested. A group of normal mothers and infants were also tested to obtain control material.

The ABO group of the erythrocytes was determined by a tube method and the Rh group was determined by the technique described previously (Boorman, Dodd and Mollison[4]), using 3 different human immune anti-Rh sera. No attempt was made to differentiate between subgroups of Rh. Usually the erythrocytes of a given family were tested against the same anti-Rh sera and in many instances they were tested directly against the mother's serum. The mother's serum was almost always tested against the same 2 Rh positive bloods and against 2 Rh negative bloods. The Rh positive bloods included one blood which was known to give consistently strong reactions with many different human anti-Rh sera; the other Rh positive blood used gave weaker reactions with most anti-Rh sera but with occasional sera gave even better reactions than the first blood. This second blood was chosen for routine tests because it appeared to be qualitatively different from the first blood and because its reactions seemed typical of the majority of Rh positive bloods. [Since this work was completed, the classification of the subgroups of Rh has advanced considerably. The first blood referred to has been tested and found to belong to subgroup Rh_2 (see Wiener [6, 32]) whereas the second blood belongs to subgroup Rh_1 (genotype, Rh_1 Rh_1; see Race and Taylor[33]).]

When anti-Rh agglutinins were found, the serum was titrated against the same test cells at intervals after delivery as the opportunity occurred.

In cases in which anti-Rh agglutinins were not found in the mother's serum, the serum was tested against 20 different group O bloods taken at random, to discover whether any atypical agglutinins were present. In all these cases in which anti-Rh agglutinins were not found, and in many of those in which anti-Rh agglutinins were found, the anti-A and anti-B agglutinins (if present) were titrated at various intervals after delivery.

The technique employed for estimating the titre of anti-A and anti-B agglutinins was that described Aubert *et al.*[8] For the titration of anti-Rh agglutinins the method was modified, firstly, by placing the tubes in the incubator for at least 2 hours instead of allowing them to stand at room temperature, and secondly, by handling the tubes gently so as to avoid breaking up the agglutinates. It should be noted that in any titration technique in which one pipette is used to make serial dilutions, a certain degree of "carry-over" is inevitable and therefore the recorded titre will be higher than the true value. (The titre of a serum is usually expressed as the reciprocal of the highest dilution in which agglutination occurs). However, in most cases only comparative and not absolute titration values are required, so that the use of one pipette is no disadvantage.

* Serological findings of 48 of these families have been reported previously (Boorman, Dodd and Mollison, 1942).

In approximately two-thirds of the cases the mother was tested within 20 days of the birth of an affected infant and in many of these repeated titrations of the serum were carried out during the 20 days after delivery. In the cases not tested within 20 days of birth, the tests were usually made within 3 months of delivery, but occasionally were not made until a year or more later.

In a few cases the patient's serum was examined at intervals during pregnancy.

Diagnostic Criteria.

In assembling a series of families in which cases of haemolytic disease of the foetus are thought to have occurred, considerable difficulties are encountered because uncertainty quite often exists with regard to the diagnosis.

The diagnosis of haemolytic disease of the newborn can usually be established with reasonable certainty if the infant is seen at the time of the illness and its blood is examined. It quite often happens, however, that no blood examination is made and if the infant recovers and is seen for the first time at a later date it is often difficult to say, on clinical grounds alone, whether it was ever affected with the disease. In the case of stillborn foetuses, these difficulties become greater. Often no thorough pathological investigations are made or, in the case of macerated foetuses, are practicable. Even when sections of the tissues are prepared there may be difficulty in getting agreement from pathologists as to the significance of a certain degree of erythroblastosis in the organs.

There is a tendency, therefore, to select the material according to the results of the serological tests. When the mother is found to have become sensitized to the Rh agglutinogen, the case is said to be one of haemolytic disease of the foetus, but when the serological findings are different, this diagnosis is rejected. This method of selection is obviously undesirable. For it will leave out of account the cases in which the disease is due to sensitization of the mother to the Rh agglutinogen but, owing to the time of examination or some other factor, anti-Rh agglutinins cannot be detected in the serum. Moreover, this selection will lead to the omission of cases in which the disease is due to sensitization of the mother to some antigen other than Rh.

In an investigation of the serological findings in cases of haemolytic disease it seems desirable to adopt definite clinical and pathological criteria for the diagnosis of the condition and then to analyse the serological results in "proved" cases. When this first assessment has been made, however, and some idea has been gained of the serological findings in a series of proved cases, it is desirable to take the further step of examining the serological findings in a series of doubtful cases and to discover what clincal and pathological findings accompany them.

In the present paper the above order has been followed. The clinical and pathological criteria adopted for the diagnosis of haemolytic disease were as follows:

1. *"Hydrops Foetalis."* Hydrops of the foetus, with anaemia and erythroblastaemia if born alive, or with evidence of erythroblastosis of the organs if stillborn. An oedematous foetus exhibiting ascites has not been considered a proved case of haemolytic disease of the foetus in the absence of haematological or pathological evidence.

2. *Stillbirth of the Foetus without Hydrops.* One family has been included because of the birth of a stillborn foetus which showed widespread extramedullary erythropoiesis.

Stillbirths occurred in many other families but in these families one or more cases satisfying criteria (1), (3), or (4) also occurred and the families have been included on account of the occurrence of these latter cases.

3. *"Icterus Gravis Neonatorum."* Onset of jaundice in an infant within 3 days of birth, fol-

lowed by the development of severe anaemia; in a few cases in which no record of blood counts was available, a history of the infant's having been severely jaundiced from the 1st or 2nd days of life onwards and having died within 10 days of birth has been accepted as evidence of affection. (It is admitted that this latter criterion is somewhat unsatisfactory).

4. *"Congenital Anaemia of the Newborn."* Onset of severe anaemia within 10 days of birth, supported by the evidence of blood examinations and in the absence of any other obvious cause such as sepsis.

1. Cases of Proved Haemolytic Disease.

(a) *Rh negative mothers.*

Among 100 families in which one or more infants were affected with haemolytic disease as defined above, the mother was found to be Rh negative in 97 cases. Among these 97 Rh negative mothers anti-Rh agglutinins were found in the serum in 93 cases. In two-thirds of these the tests were made within 20 days of delivery. In the 4 cases in which no anti-Rh agglutinins were found in the serum, the tests were made 7 days, 9 days, 21 days and approximately 11 years after delivery respectively.

In this group of 97 families in which the mother was Rh negative, 79 affected infants were tested and all were found to be Rh positive. Forty-five fathers were tested and all were Rh positive.

(b) *Rh positive mothers.*

In the sera of the 3 Rh positive mothers immune agglutinins incompatible with the foetal erythrocytes were found in every case. In one of these instances the incompatible agglutinin was atypical. In this case, mother, father and infant were all group A Rh positive, but the mother's serum contained an agglutinin which acted upon the infant's and father's red cells and also upon approximately 1 in 3 bloods of groups A and O taken at random. In the other 2 cases in which the mother was Rh positive the incompatible agglutinin was an immune anti-B. In one case the titre reached the exceptionally high value of 8 million at the peak of the response, but in the other the maximal titre attained was 32,000.

(c) *Affected and Unaffected Siblings in families in which one or more proved cases of haemolytic disease occurred.*

In 88 of these 100 families some data about all the siblings in the family were available. In these 88 families there was a total of 303 siblings. Of these, 111 were normal, 130 had haemolytic disease of the newborn (as defined by criteria (3) and (4) above); 8 had hydrops foetalis (as defined by criteria (1) above); 6 others died within a few hours of birth and the remaining 48 were born dead.

Among the 88 families, 55 of the first-born infants were normal (in all these cases the mother was Rh negative). Some typical examples of families in which the birth of one normal infant was followed by the birth of one or more affected infants, are given in Table I. In 13 cases the firstborn infant was tested and in every case was found to be Rh positive.

In 25 families, 2 or more normal children were born before the birth of an affected infant. Details of some of these families are given in Table II. In one family in which 6 normal children were born in succession, before the birth of an infant affected with icterus gravis, 5 of the normal siblings were tested and all were found to be Rh positive. The 7th child, also Rh positive, was affected.

It will be noted that the disease does not necessarily become more severe in successive siblings. In family 9, for example, the birth of 10 infants in succession, all of whom died with icterus gravis within a few days of birth, was followed by the birth

TABLE I.

Some Examples of Families in which First-born Infant was Normal but in which the Second Infant was Affected with Haemolytic Disease.

(One family included in which craniotomy was performed on first child because of disproportion).

Family serial No.	Serological findings: Mother Erythrocytes	Mother Serum	Father Erythrocytes	Siblings: Year of birth, clinical condition and serological findings 1	2	3	4	5	6
1	ARh−	Anti-Rh	ORh+	1932 N ARh+	1942 I.G. recovered ORh+				
2	ORh−	Anti-Rh	ORh+	1930 N	1938 H.A. recovered ORh+	1942 I.G. recovered ORh+			
24	ARh−	Anti-Rh	ORh+	1938 N ORh+	1940 I.G. died	1942 H.F.			
16	ORh−	Anti-Rh	—	1936 N	1940 ?I.G. recovered	1942 twins H.F. both ARh+			
39	ARh−	Anti-Rh	ORh+	1933 Craniotomy for dispro-portion	1935 ?I.G. died	1936 S.B. 8/12	1937 S.B. 7/12	1942 I.G. died	
38	ORh−	Anti-Rh	ORh+	1930 N	1937 I.G. recovered	1937 S.B. 3/12	1940 I.G. died	1942 I.G. died ORh+	
9	ARh−	Anti-Rh	—	1921 N ORh+	I.G. died	I.G. recovered	I.G. died	I.G. recovered Kern-icterus ARh+	
				I.G. died	I.G. died	I.G. died	I.G. died	I.G. died	
				I.G. died	I.G. died	I.G. died	I.G. died	I.G. recovered ARh+	

N. = Normal.
H.F. = " Hydrops Foetalis " as defined by criteria (1) in text.
I.G. = " Icterus gravis neonatorum " as defined by criteria (3) in text.
H.A. = " Haemolytic anaemia of the newborn " as defined by criteria (4) in text.
S.B. = Stillbirth.

TABLE II.

Some Examples of Families in which the Birth of at least Two Normal Infants Preceded the Birth of an Infant Affected with Haemolytic Disease.

Family serial No.	Serological findings, Mother		Siblings: Year of birth, clinical condition and serological findings					
	Erythro-cytes	Serum	1	2	3	4	5	6
13	ORh−	Anti-Rh	1931 N ORh+	1933 N ORh+	1935 S.B.	1937 jaundiced ORh+	1940 I.G. died	1942 S.B. oedematous
17	ORh−	Anti-Rh	1938 N ORh+	1940 N ORh+	1942 I.G. recovered ARh+			
25	ARh−	Anti-Rh	1939 N	1940 N	1942 twins I.G. both died, both ARh+			
11	ORh−	Anti-Rh	1929 N ORh+	1931 N ORh−	1936 N ORh−	1938 N ORh+	1940 N ORh+	1942 I.G. recovered ORh+
29	ORh−	Anti-Rh	1928 N died later	1930 N ORh−	1934 N ARh−	1938 N ARh+	1942 I.G. recovered ARh+	
37	ARh−	Anti-Rh	1934 N	1936 N	1940 I.G. recovered (kern- icterus) ORh+			
47	ARh−	Anti-Rh	1921 N 1933 I.G. died	1922 N 1934 S.B. 9/12	1924 N 1936 S.B. 7/12	1926 N 1942 S.B. 9/12	1928 N	1931 I.G. died
43	ARh−	Anti-Rh	1923 N 1942 I.G. recovered ORh+	1925 N ARh+	1927 N ORh+	1929 N Rh+	1931 N ARh+	1933 N ORh+
45	ORh−	Anti-Rh	1940 N ORh+	1941 N twins (ORh+ (ARh+	1942 I.G. recovered ORh+			

TABLE II. (*Continued*).

Family serial No.	Serological findings, Mother		Siblings: Year of birth, clinical condition and serological findings					
	Erythro-cytes	Serum	1	2	3	4	5	6
51	ARh−	Anti-Rh	1931 N	1934 N	1934 S.B. 5/12	1939 H.A. recovered	1942 S.B.	
54	ORh−	Anti-Rh	1935 N	1937 N	1939 I.G. died	1942 I.G. recovered ORh+		
70	ARh−	Anti-Rh	1934 N died later	1937 N ARh+	1943 I.G. recovered ARh+			
75	ARh−	Anti-Rh	1934 N	1937 N	1943 I.G. recovered ARh+			
64	ARh−	Anti-Rh	1931 N	1933 N	1935 N	1937 N	1939 jaundiced recovered	1943 I.G. recovered ARh+

of an infant which, although affected, recovered. Again, in family 90 the birth of 3 infants, all of whom died of icterus gravis within a few days of birth, was followed by the birth of an infant which, although affected with icterus gravis, recovered spontaneously. The next infant, however, died of icterus gravis within a few days of birth. It is worth mentioning that in this family it was at first reported that the 3rd child which recovered had always been perfectly normal. Only when the mother was directly questioned did it emerge that the 3rd child had been seriously jaundiced from the 1st day of life for many weeks and had only recovered after a critical illness. This illustrates quite well the difficulty which is experienced in obtaining reliable information about these families.

In 17 families the 1st pregnancy ended in a miscarriage or stillbirth or in the birth of an infant which died within 24 hours of delivery. In only 4 of these 17 cases could the cause of death be definitely ascribed to haemolytic disease according to the criteria mentioned above. Some details of these 4 cases are given in Table IV. Of the remaining 13 cases in which the cause of death of the firstborn infant could not be determined, the histories were as follows: miscarriages during the first 6 months of pregnancy: 5 cases; stillbirths during the last 3 months of pregnancy: 5 cases; death within 24 hours of delivery: 3 cases. In 6 other families the firstborn infant was affected with haemolytic disease but recovered. Details of these families are also given in Table IV.

Thirty normal siblings (including the 13 firstborn infants mentioned above), born prior to the birth of an affected infant, were tested. Of these 26 were Rh positive and 4 Rh negative.

TABLE III.

Some Examples of Families in which the Birth of a Normal Infant Followed the Birth of One or More Infants Affected with Haemolytic Disease (According to Certain Defined Criteria).

Family serial No.	Serological findings, Mother		Siblings: Year of birth, clinical condition and serological findings						
	Erythrocytes	Serum	1	2	3	4	5	6	7
35	ORh−	Anti-Rh	1937 N ORh+	1939 I.G. died	1941 N ARh−	1942 N ARh−			
41	ARh−	Anti-Rh	1922 N	1927 N	1933 N ARh+	1938 N	1939 I.G. died	1941 N ARh−	1942 N ORh−
63	ARh−	Anti-Rh	1926 Misc. 4½ mths.	1927 I.G. died	1930 N ARh−	1942 I.G. recovered ARh+			
83	ORh−	Anti-Rh	N	I.G. Kern- icterus	N ORh−				

N.B.—Family 60, in which the birth of an infant who died of "icterus gravis" was followed by the birth of an infant which was mildly jaundiced and recovered, is not included in this table because there was some doubt as to whether this latter infant was or was not affected with haemolytic disease.

In 5 families the birth of an affected infant was followed by the birth of one or more normal children. In 4 families the normal children tested were all found to be Rh negative. In the fifth family, the normal child was Rh positive. It must be added, however, that in this case there was a suspicion that the infant was very mildly affected with haemolytic disease.

(d) *Changes in Titre of Immune Anti-Rh Agglutinins during Pregnancy and after delivery.*

In 7 cases a mother who had previously given birth to an infant known to have been, or thought to have been affected with haemolytic disease, was tested repeatedly during a subsequent pregnancy. In every instance anti-Rh agglutinins were found in her serum. In 2 of the 7 cases a progressive increase in titre was noted during pregnancy, and in both of these an affected infant was subsequently born. In 3 other cases an affected infant was subsequently born but no change in the titre of the anti-Rh agglutinins was detected. In the remaining 2 cases there was no change in the titre of the anti-Rh agglutinins and the infant, when born, proved to be Rh negative and unaffected. Evidently the formation of anti-Rh agglutinins in the mother's serum in these cases had been stimulated by a previous pregnancy in which an Rh positive infant had been carried.

In the great majority of the 100 cases some increase in titre of anti-Rh agglutinins was observed *following* the birth of an Rh positive affected foetus and the peak of this response was attained between the 8th and 20th days after delivery in almost every case. (Details of these and other immune responses in connexion with pregnancy are being published elsewhere).

TABLE IV.

Some Examples of Families in which the Firstborn Infant was Affected with Haemolytic Disease (According to Certain Defined Criteria).

Family serial No.	Serological findings			Siblings: Year of birth, clinical condition and serological findings			Notes
	Mother		Father				
	Erythrocytes	Serum	Erythrocytes	1	2	3	
30	ARh−	Anti-Rh	ORh+	1942 H.D. recovered ARh+			
32	ARh−	Anti-Rh	ARh+	1942 I.G. died			
34	ARh−	Anti-Rh		1933 I.G. died	1936 H.F. died	1937 H.F. died	
42	ORh−	Anti-Rh	ARh+	1942 I.G. recovered ARh+			
71	ARh−	Anti-Rh		1942 I.G. recovered ORh+			
87	ORh−	Anti-Rh		1942 I.G. recovered ORh+			
90	BRh−	No anti-Rh	ORh+	I.G. died I.G. recovered BRh+	I.G. died I.G. died	I.G. died	
4	ORh−	No anti-Rh Immune Anti-A		1942 H.A. recovered ARh+			Immune anti-A; titre 8,000 at peak
20	ARh+	Immune Anti-B	BRh+	1942 I.G. died			Immune anti-B; titre 32,000 at peak
74	ORh+	Immune Anti-B	BRh+	1942 I.G. recovered BRh+			Immune anti-B; titre 8,000,000 at peak

DISCUSSION OF SEROLOGICAL FINDINGS.

Findings of anti-Rh agglutinins in sera of Rh negative mothers.

It was mentioned above that Levine, Katzin, Vogel and Burnham,[2] only found anti-Rh agglutinins in the sera of a proportion of Rh negative women whose infants were affected with haemolytic disease of the foetus. Of 141 such mothers, anti-Rh agglutinins were found in the sera of 42.

Among 70 cases who were examined within 2 months of delivery, however, the proportion was much higher, i.e. 33 out of 70. Wiener[6] also has stated "in more than half the cases anti-Rh antibodies are not detectable" and has supported this statement with the reference "unpublished observations." It will be evident that the experience recorded in this paper is considerably different since anti-Rh agglutinins were found in 93 out of the 97 Rh negative mothers tested. This may be due in part to the fact that many of the present cases were examined within a short time of delivery. On the other hand, among 37 cases examined at 2 months or later after delivery, all but 1 still had detectable anti-Rh agglutinins. It must therefore be concluded that the technique used in the present tests was more sensitive than that employed by the authors referred to above. In this connection it is of interest that Race, Taylor, Cappell and McFarlane[9] who used a technique almost identical with ours, also found that a high proportion of the sera of Rh negative women, whose infants were affected with haemolytic disease, contained anti-Rh agglutinins; (they were demonstrated in 38 out of 44 sera, many of which were not examined for some months or more after delivery).

The observation of this high incidence of anti-Rh agglutinins in the sera of Rh negative mothers whose infants are affected with haemolytic disease suggests that, provided the mother's serum has been examined within say, 20 days of delivery, and a sensitive technique has been used for the examination, failure to find anti-Rh agglutinins in the serum of an Rh negative mother should be interpreted as meaning that her infant is probably not affected with haemolytic disease.

As mentioned above, in one family, mother, father and infant were all Rh positive, but the mother's serum agglutinated the erythrocytes of the infant and father and also approximately 1 in 3 Rh positive bloods (groups O and A) taken at random. It was observed that the serum only agglutinated 2 out of 45 Rh negative bloods. Subsequently, it was possible to identify this agglutinin as anti-Rh_2 (Wiener and Sonn[10]); fuller details of its reactions are given by Race, Taylor, Boorman and Dodd[7] in a note in which the serum is described as *K*. The fact that this agglutinin was responsible for the destruction of the foetal erythrocytes was demonstrated by transfusing the infant with a mixture of 2 bloods, one of which was agglutinated by the mother's serum and the other of which was not. It was found that the "incompatible" erythrocytes were far more rapidly destroyed in the infant's circulation than were the "compatible" erythrocytes (Mollison.[11])

In 2 families, the mother's serum was found to contain potent anti-B agglutinins incompatible with the foetal erythrocytes, the titre of the agglutinins being 32,000 and 8,000,000 respectively. It seems probable that the affection of the infant in these cases was caused by these immune agglutinins (see discussion below).

SUMMARY OF FINDINGS IN 100 PROVED CASES OF HAEMOLYTIC DISEASE OF THE FOETUS.

Immune agglutinins, incompatible with the foetal erythrocytes were found in 96 out of the 100 cases. In 93 cases the agglutinin was anti-Rh; in one other case, the agglutinin was identified as anti-Rh_2 and in the remaining 2 cases it was anti-B. In the latter 2 cases the potency of the agglutinins was far greater than that observed in the majority of cases in a series in which the infant was normal. In the following section, therefore, the finding of immune agglutinins of these kinds, incompatible

with the foetal erythrocytes has been taken as highly suggestive evidence that the foetus was affected with haemolytic disease.

It is realized that this method of selection may lead to the exclusion of some genuine cases for, as mentioned above, anti-Rh agglutinins are not always found in the sera of Rh negative mothers whose infants are affected with haemolytic disease, even when the time of examination is favourable. When the mother's serum is examined many months or years after delivery, immune agglutinins will often have disappeared and serological tests are then incapable of affording decisive evidence of previous iso-immunization. Few such cases, however, have been included and the great majority were examined within a short time of delivery.

II. Cases of Stillbirth or Neonatal Death (within 48 Hours of Delivery) in Families in which no Proved Case of Haemolytic Disease Occurred.

Seventy mothers who had had one or more miscarriages or stillbirths were tested. In 11 cases anti-Rh agglutinins were found in the serum; on the basis of the results in Section I, the death of the foetus in these 11 cases is considered to have been due to haemolytic disease. In three other cases, very potent anti-A or anti-B agglutinins were found (peak titres 500,000, 1,000,000 and 32,000). It is considered uncertain whether or not these foetuses were affected with haemolytic disease (see discussion below).

The failure to find immune agglutinins in the remaining 56 cases renders it unlikely that in more than a few of these instances (at the most) was the foetus affected with haemolytic disease, since the great majority of these cases were examined within 20 days of delivery. This conclusion receives further support from the observation that only 6 of these 56 mothers were Rh negative. In the case of one of the 6 Rh negative mothers, iso-immunization may have occurred, but since the serum was not examined until 5 years after the last delivery a definite opinion could not be given. The other 5 Rh negative mothers were tested within 14 days of delivery.

Some details of the 11 families in which the stillbirth or miscarriage was apparently attributable to iso-immunization are given in Table V. It will be noted that in 5 of the cases the diagnosis of "hydrops foetalis" had been made from the appearance of the foetus. In these cases, however, no pathological examination was carried out and according to the criteria adopted these cases could not therefore be included as "proved instances of haemolytic disease of the foetus" in section I. In the remaining 6 families oedema of the foetus was not recorded and the infant was macerated or outwardly normal. In this group of 11 cases, the dead foetus was born at the 7th month of pregnancy in all but one instance. In this latter instance (family 84) a stillbirth at $7\frac{1}{2}$ months of pregnancy was followed by miscarriages at $5\frac{1}{2}$ months and $3\frac{1}{2}$ months respectively.

Among the group of 56 cases in which the stillbirth or miscarriage did not appear to be due to haemolytic disease, the birth of the dead foetus occurred in many of the cases at an early stage in pregnancy (i.e. within the first 6 months). In some, however, the birth occurred at a late stage and in a few the diagnosis of hydrops foetalis was considered on clinical grounds. The following case may be quoted as an example: First 2 pregnancies, normal infants; 3rd pregnancy, macerated foetus exhibiting gross ascites delivered at term. An examination of the blood or tissues was not carried out, but serological tests showed that the mother and foetus were both group O, Rh positive and no incompatibility could be detected between the

TABLE V.

Some Examples of Families in which More than One Stillbirth (or Miscarriage) occurred and in which the Serological Findings suggested that the Foetal Death was due to Haemolytic Disease.

Family serial No.	Serological findings, Mother		Siblings: Clinical condition and serological findings			
	Erythrocytes	Serum	1	2	3	4
21	ARh−	Anti-Rh	N	N	S.B.*	
22	ORh−	Anti-Rh	N, ORh+	S.B.	S.B.*	
26	ORh−	Anti-Rh	N	S.B., 7/12	S.B., 8/12	
33	ARh−	Anti-Rh	N S.B.	N N	N S.B.*	N
50	ARh−	Anti-Rh	S.B., F.T.			
57	ARh−	Anti-Rh	N	died at 12 hrs.	S.B., F.T.	
58	ARh−	Anti-Rh	N	S.B.*		
82	ORh−	Anti-Rh	S.B.	died 1st day		
84	ARh−	Anti-Rh	S.B., 7½/12	S.B., 5½/12	S.B., 3½/12	
92	ARh−	Anti-Rh	N	S.B.*		
94	ARh−	Anti-Rh	N	S.B., 7/12	S.B.*	

* Clinical diagnosis "Hydrops foetalis."
F.T. = Full Term.

mother's serum and the infant's erythrocytes. Moreover, the mother's serum, when examined again 10 days after delivery, did not show any evidence of atypical agglutinins. It therefore appeared unlikely that the foetus was affected with haemolytic disease.

Discussion.

In 59 out of 70 cases in which a mother had given birth to one or more stillborn foetuses, or had miscarried on one or more occasions, no evidence of iso-immunization to the Rh factor could be obtained. In the remaining 11 cases, on the other hand, there seemed little doubt that the death of the foetus was due to haemolytic disease, for iso-immunization of the mother to the Rh agglutinogen was demonstrated.

Although on the whole the cases of foetal death due to haemolytic disease occurred late in pregnancy, and the cases not attributable to haemolytic disease were mostly miscarriages during the early months of pregnancy, the history alone is an unreliable guide in the individual case, since exceptions to both these rules occur. Among some of the 59 cases in which evidence of iso-immunization to the Rh factor was not obtained, death of the foetus occurred at the 7th or 8th month of pregnancy in several instances. Conversely, in one family included in Section I (see Table I), a mother gave birth at the 5th month to a stillborn foetus which exhibited the typical features of hydrops foetalis. (We are indebted to Dr. J. R. Gilmour for this opinion. He found lipoid infiltration of the suprarenal cortex and points out that this change only occurs in hydrops foetalis).

Serological tests are likely to prove valuable in deciding in a given case whether or not foetal death is attributable to haemolytic disease.

III. Serological Tests in Cases in which the Infant was apparently Normal.

Sixty infants developing "physiological jaundice" were tested, together with their mothers. Any infant developing jaundice within the first 5 days of life was considered to be affected with "physiological jaundice," provided that there were none of the classical features of "icterus gravis" as defined above, and provided that there was reasonable evidence that the jaundice was not caused by syphilis, sepsis or congenital obliteration of the bile ducts.

Rh Group Differences.

Six of the 60 mothers were Rh negative. In 3 of these cases, anti-Rh agglutinins were found in the mother's serum (all 6 cases were tested repeatedly during the 20 days following delivery). One of these 3 cases occurred in a family described above (see Table II) in which a previous infant had been affected with "icterus gravis." The present infant may also have been affected (though mildly) with haemolytic disease because its haemoglobin value was only 92 per cent 8 days after delivery and a blood film made on the 3rd day of life showed as many as 15 nucleated red cells per 100 leukocytes. Unfortunately, the child could not be examined again after the 8th day. However, it is known that it was perfectly healthy at the 3rd month of life so that it cannot have been very seriously affected. In the other 2 cases the infant only developed the mildest degree of jaundice and repeated examination of blood films never revealed any abnormality so that the diagnosis of haemolytic disease appeared to be definitely excluded and the jaundice of the infant could not reasonably be ascribed to this cause.

ABO Group Differences.

Among the first 25 cases tested, the mother's serum was found to be incompatible with the infant's erythrocytes with respect to the anti-A and anti-B agglutinins in as many as 13 cases. Since the expected incidence of this kind of incompatibility (i.e. due to anti-A or anti-B agglutinins) is only one in 5 births (according to a figure kindly supplied by Dr. G. L. Taylor), it was thought that this finding was suggestive of some relationship and that some cases of physiological jaundice might in fact be mild cases of haemolytic disease of the newborn due to destruction of the foetal erythrocytes by anti-A or anti-B agglutinins (see Boorman, Dodd and Mollison[4]).

In the next 32 consecutive cases tested, however (excluding the 3 cases in which anti-Rh agglutinins were found in the mother's serum), the incidence of this kind of incompatibility was only 7, almost exactly the expected figure in a random sample of cases. Thus in the majority of cases of "physiological jaundice" no incompatibility between the mother's serum and the infant's erythrocytes could be detected.

Further evidence was obtained from another group of cases in which routine tests were made on the bloods of mothers and infants taken at random. In 26 cases in which the mother's serum was incompatible with the foetal erythrocytes, the infant did not develop severe jaundice in a single case and developed mild transient jaundice in only a small number of instances. In 16 out if these 26 cases there was evidence of an immune response following the birth of a child, the highest titres attained falling between 256 and 11,000.

There is, therefore, no evidence that "physiological jaundice" of the newborn is, in the great majority of cases, in any way connected with the presence of incompatible agglutinins in the mother's serum. At the same time it seems evident that mild cases of haemolytic disease of the newborn (with jaundice) may occasionally be mistaken for cases of "physiological jaundice" and serological tests are often useful in indicating whether a given case is likely or unlikely to be one of haemolytic disease of the newborn. One doubtful case has been quoted above. The following case may be quoted as a further example: Family 42. First infant healthy at birth but developed slight jaundice within 24 hours and by the 2nd day was very jaundiced. By the 14th day of life, the jaundice had practically faded. A blood count showed R.B.C. 3,950,000 per c.mm., haemoglobin 80 per cent. During the next 11 days the haemoglobin fell to 64 per cent, however, and serological tests showed that the mother was Rh negative, the infant Rh positive and the mother's serum contained weak anti-Rh agglutinins. It thus seemed clear that the infant was mildly affected with haemolytic disease of the newborn.

Value of Serological Tests in Diagnosis.

1. *Rh Typing and Detection of Anti-Rh agglutinins.*

The point has already been made above that the mere demonstration that the mother is Rh negative and the infant Rh positive cannot be regarded as satisfactory diagnostic evidence because this combination frequently occurs without the infant being affected. On the other hand, in families in which one or more infants were affected with haemolytic disease the mother was Rh negative in 97 out of 100 cases and in these families all the affected infants tested were Rh positive. Therefore, when the diagnosis is in doubt this finding must be considered suggestive, although not conclusive evidence. At the same time it will be clear that the finding that the mother is Rh positive in a case in which the infant is suspected of being affected with haemolytic disease does not exclude the diagnosis but is an indication to make further tests upon the mother's serum.

Immune anti-Rh agglutinins were found in the sera of 93 of the 97 Rh negative mothers mentioned above. Such anti-Rh agglutinins were found in the sera of only 3 Rh negative mothers whose Rh positive infants were simply affected with physiological jaundice, and have not been found in a single case in a control series of approximately 50 Rh negative mothers whose Rh positive infants were normal. Thus among 96 cases in which the mother's serum contained anti-Rh agglutinins, incompatible with the foetal erythrocytes, the infant was affected in 93 cases. Far more important, therefore, than the mere demonstration that the mother is Rh negative and the infant Rh positive, is the demonstration of immune anti-Rh agglutinins in the mother's serum.

It has already been stated that atypical anti-Rh agglutinins (anti-Rh_2) were found in the serum of one Rh positive mother whose infant was affected with haemolytic disease. Since the completion of this series, two further exactly similar cases have been encountered (Boorman and Mollison[12]).

The classification of the Rh subgroups is extremely complicated (see Wiener[6] and Race, Taylor, Boorman and Dodd[7]), and because of this the most reliable method of testing for unusual anti-Rh agglutinins in the mother's serum is to test the latter directly against the infant's erythrocytes. However, all the varieties of anti-Rh agglutinin so far described have reacted with Rh_1, Rh_2 or Rh negative ery-

throcytes. As explained above, all the sera examined in this series were tested against bloods of these 3 types.

2. *Detection of other Atypical Agglutinins.*

Although so far as we know, no case has yet been described in which immunization of a woman during pregnancy to an agglutinogen other than A, B or Rh (including subgroups of the A and Rh factors), has been the cause of haemolytic disease in her infant, the theoretical possibility of immunization to such factors as M or N remains and this is a further reason for testing the mother's serum directly against the infant's erythrocytes wherever possible.

When, owing to the existence of incompatibility between the mother's serum and the infant's erythrocytes due to the presence of anti-A or anti-B agglutinins in the former, the direct test is incapable of revealing the presence of atypical agglutinins, or when the infant's erythrocytes are not available, it has therefore been our practice to test the mother's serum against 20 random bloods of her own group or of group O.

3. *Titration of Immune Anti-A and Anti-B Agglutinins.*

It is not unusual for immune anti-A and anti-B agglutinins to be present in the mother's serum after pregnancy (Dienst,[13] Jonsson,[14]) when the infant's erythrocytes contain the A or B agglutinogens and the mother's erythrocytes do not. However, the titre attained by these immune agglutinins varies very considerably.

Among the 100 proved cases of haemolytic disease there were 2 in which the only agglutinin in the maternal serum incompatible with the infant's erythrocytes at 37°C., was an immune anti-B. Therefore it was concluded that this immune agglutinin was responsible for the disease in these 2 cases. In one instance, the anti-B titre reached the exceptionally high value of 8,000,000, while in the other, the highest value attained was 32,000.

In 3 of the 70 mothers who had had one or more miscarriages or stillbirths, very potent immune anti-A or anti-B agglutinins were found in their sera. The titres attained in these cases were 500,000 and 1,000,000 and 32,000. In the first 2 cases postmortem examination of the foetal tissues was carried out; in one there was no evidence of extra-medullary erythropoiesis and in the other the tissues were so macerated that no conclusions could be drawn from the sections.

Only one other immune anti-A or anti-B agglutinin of such potency was found. This was an immune anti-A in the serum of a mother whose infant was apparently normal. However, this infant (group A) suffered a severe haemorrhage due to the slipping of the ligature from the umbilical cord within a few minutes of birth. A large transfusion of blood (group O) was administered so that the subsequent satisfactory progress cannot be taken to exclude completely the possibility that this infant was to some extent affected with haemolytic disease of the newborn. The titre in this case was 500,000.

The immune anti-A or anti-B agglutinins (incompatible with the infant's erythrocytes) in the sera of 16 mothers whose babies were normal were titrated repeatedly during the 21 days following delivery. The highest titres attained varied between 256 and 4,000.

From these figures it will be seen that immune anti-A or anti-B agglutinins of a titre of 32,000 or higher were found in one case in which the infant was normal, in 2 cases in which it was definitely affected with haemolytic disease and in 3 cases in which the infant was stillborn without apparent cause. Reasons have already

been given above for believing that in the 2 cases of haemolytic disease referred to the immune anti-B agglutinins in the mothers' sera were responsible for the disease. Evidently many other factors are involved besides the potency of the agglutinins, and therefore the finding of such high titre immune agglutinins in obscure cases cannot be regarded as diagnostically decisive.

The significance of serological tests in suspected cases of haemolytic disease may be summarized as follows:

(a) *Diagnosis very probable.*

(1) When the mother is Rh negative and her foetus is Rh positive, and when anti-Rh agglutinins are found in the mother's serum.

(2) When the mother is Rh positive and her serum contains any other atypical agglutinins, related or unrelated to anti-Rh, incompatible with the foetal erythrocytes and active at 37°C.

(b) *Diagnosis less probable.*

(1) When the mother's serum contains exceptionally potent anti-A or anti-B agglutinins incompatible with the foetal erythrocytes.

(2) When the mother is Rh negative and the foetus Rh positive but the mother's serum does not contain any anti-Rh agglutinins.

(c) *Diagnosis improbable.*

When the mother is Rh positive and her serum is compatible with the infant's erythrocytes, or the incompatibility is merely due to anti-A and anti-B agglutinins of ordinary potency.

N.B. (b) and (c) only apply when the mother's serum is examined by a sensitive technique and the examination is carried out between say 8 and 20 days after delivery. When this condition is not complied with, serological tests are incapable, in the present state of knowledge, of giving a decisive answer in any particular case to the question whether iso-immunization has occurred and whether the infant has or has not been affected with haemolytic disease. However, when the mother is Rh positive the diagnosis becomes less likely and when there is also no potential incompatibility between the mother's serum and the infant's erythrocytes due to Rh subgroup or ABO group differences, the diagnosis becomes still less likely, although it is not absolutely excluded.

Value of Serological Tests in Prognosis.

Knowledge of the relationship between sensitization of the mother to the Rh agglutinogen and affection of the foetus with haemolytic disease may lead to the performance of Rh tests upon mothers during pregnancy as a routine. Although it is clear that the outlook for Rh negative mothers as a group is less favourable than that for Rh positive mothers, the finding that a given mother is Rh negative is not in the individual case of very great significance. If it is true that approximately 1 in 400 foetuses are affected with haemolytic disease (Javert[15]) and if, for the moment, it is assumed that these are only born to Rh negative mothers, the chances that any given foetus of an Rh negative mother taken at random will be affected are only approximately one in sixty. The finding of anti-Rh agglutinins in the serum of a pregnant woman has to be interpreted in the light of her previous history. If the woman has previously given birth to an infant affected with haemolytic disease, the anti-Rh agglutinins may remain in her serum for many years, and their presence does not, therefore, necessarily mean that the infant at present in utero is Rh positive. Nevertheless, since in practice once a mother has given birth to an infant affected

with haemolytic disease, her subsequent foetuses are very likely to be affected also, it is clear that when anti-Rh agglutinins are found that the outlook will usually be bad. Exceptions will be due either to the fact that the foetus in utero is Rh negative or in rare cases that although Rh positive it escapes being affected.

As explained above, changes in titre of anti-Rh agglutinins during pregnancy are not in the present state of knowledge very informative. Although a rise in titre during pregnancy will probably always indicate that the foetus in utero is Rh positive, failure of the anti-Rh agglutinins to increase in titre does not imply that the foetus is Rh negative and so will escape being affected.

The main importance of making Rh grouping tests during pregnancy as a routine is the detection of Rh negative women so as to ensure that if they require a blood transfusion they shall not receive Rh positive blood. The transfusion of Rh positive blood to any Rh negative woman of childbearing age may have one of two unfortunate consequences. If the woman has already been sensitized to the Rh agglutinogen she may suffer a severe haemolytic reaction. Alternatively, if she has not yet been sensitized to the Rh agglutinogen, she may become sensitized by the transfusion, so that in a subsequent pregnancy, she becomes more likely to affect her foetus.

In this series, as mentioned above, 55 out of 88 first children in the families analysed were normal and only 11 first children were definitely affected with haemolytic disease. (In the remaining 22 cases the cause of death was not certainly known). It has long been recognized that in families in which haemolytic disease of the foetus occurs, that the first child usually escapes the disease. It is of interest that in the 2 instances in which it appeared likely that the anti-A or anti-B agglutinins were responsible for the death of one or more foetuses, that the first foetus in the family was affected in each case. This does not seem surprising since the anti-A and anti-B agglutinins are already present at the start of the first pregnancy, whereas in the cases due to immune anti-Rh agglutinins, no anti-Rh agglutinins at all exist at the beginning of a first pregnancy,* provided that the mother has not become immunized as a result of receiving transfusions of Rh positive blood.

It has usually been taught that in families in which haemolytic disease of the foetus occurs, although a mother may have two or even more normal children first, that once she has started having affected children, all subsequent children will be affected. When the mode of inheritance of the Rh factor was investigated, however, (Landsteiner and Wiener[17]) it became clear that an Rh negative (*rhrh*) woman with an Rh positive husband would have all Rh positive children if the husband was homozygous (*RhRh*), but that if he were heterozygous (*Rhrh*) that there would be an even chance that any given child would be Rh negative. (In this discussion the symbol *Rh* stands for any Rh + gene, regardless of subgroups.) In such families it would be expected that once the mother had become sensitized to the Rh agglutinogen, that the infants would be affected or unaffected according to whether they were Rh positive or Rh negative. Four examples of this kind of family have been given above.

According to figures supplied by Landsteiner and Wiener,[17] in families in which the father is Rh positive and the mother Rh negative, the proportion of Rh positive to Rh negative siblings is approximately 5 to 2. In testing families in which some of

* One case in which naturally occurring anti-Rh agglutinins were found in the serum of a child who had never received a transfusion has been described by Diamond.[16]

the Rh positive children are affected with haemolytic disease, however, this proportion of Rh positive to Rh negative siblings will no longer be expected for the following reasons. As mentioned above, usually the first Rh positive child and sometimes subsequent Rh positive children escape the disease in families in which it occurs later. Therefore small families in which some of the siblings are Rh negative, will be more likely to escape the disease altogether than small families in which all the siblings are Rh positive. Therefore, at least when testing small families in which haemolytic disease has occurred, it will not be surprising if the great majority of the unaffected siblings are found to be Rh positive. The finding in this series that 24 out of 27 unaffected siblings were Rh positive is compatible with this view, although the numbers are too small to be significant. Race, Taylor, Cappell and McFarlane[9] also found very few Rh negative siblings in families in which the birth of affected Rh positive siblings occurred.

Although in families in which all the siblings are Rh positive, and one or more affected siblings have been born, subsequent Rh positive siblings may escape the disease or have it in a mild form and recover, nevertheless in general it is clear that the prognosis for a family in which the birth of an infant affected with haemolytic disease has occurred is undoubtedly very bad.

Discussion.

The fact that the Rh positive infant may be unaffected despite the presence of anti-Rh agglutinins in the mother's serum is not perhaps from a theoretical point of view any more remarkable than that a group A infant may be unaffected by the presence of quite potent anti-A agglutinins in the mother's serum. The effect on the foetus presumably depends chiefly upon three factors: (i) the titre of the agglutinins in the mother's serum; (ii) the permeability of the placenta; (iii) the amount of extracorpuscular group-specific antigen.

In the present series it was noted that the first factor, the titre of agglutinins in the mother's serum was certainly not the only factor, because in some cases the infant was affected with hydrops foetalis (generally accepted as the most severe manifestion of haemolytic disease of the foetus), although the mother's serum contained only weak anti-Rh agglutinins. Conversely, the two highest titres of anti-Rh agglutinins were observed in the serum of mothers whose infants survived until the 8th and 10th day of life respectively without any treatment and one of whom afterwards made an apparently complete recovery.

With regard to the permeability of the placenta, it can only be said that variations between one case and the next do not appear to depend upon any accident occurring in a particular pregnancy, because once a woman has become sensitized to the Rh agglutinogen, subsequent Rh positive foetuses are almost always affected with haemolytic disease.

It is generally agreed that when there is an incompatibility between the mother's serum and the infant's erythrocytes with regard to the A and B agglutinogens, the low incidence of haemolytic disease of the foetus is due to the absorption of the maternal antibodies by the A and B group specific substances in the foetal tissues and body fluids, before they can affect the infant's red cells. As anti-Rh agglutinins seem to cause haemolytic disease of the foetus so much more frequently it has been generally concluded that the Rh group specific substance is probably confined to the erythrocytes (Levine and Katzin[18]; Wiener and Forer[19]).

Boorman and Dodd[20] however have shown that the quantitative distribution of

the Rh group specific substance in tissues is similar to that of A and B, but whereas the A and B substances in tissues are readily soluble in water (in 'secretors') the Rh substance in tissues is apparently not water-soluble. They have, therefore, concluded that the absorption of agglutinins crossing the placenta from the maternal to the foetal circulation is probably effected by the soluble group specific substances contained in the body fluids and that the tissue antigens play little if any part. On the other hand, in about 50 per cent of salivas from Rh positive individuals very small amounts of Rh group specific substance could be detected. This suggests that in some individuals there is a small amount of water-soluble body fluid Rh substance which may afford a measure of protection.

Examples have been given above of 2 cases in which despite the presence of anti-Rh agglutinins in the serum of the mother at the time of delivery, an Rh positive infant was unaffected with haemolytic disease. Examples have also been given of cases in which infants of group A and B were observed to be unaffected despite the presence of quite potent anti-A and anti-B agglutinins in the serum. Conversely, in one of the cases in which the infant appeared to be affected with haemolytic disease due to the action of anti-B agglutinins, the titre of the anti-B agglutinins in the mother's serum only reached 32,000 at the peak of the immune response. These findings suggest that the potency of the agglutinins in the mother's serum, although important, is by no means the only factor determining the affection of the foetus with haemolytic disease. It appears that in cases in which the mother is Rh negative her ability to form immune anti-Rh agglutinins may be the most important single factor in the causation of haemolytic disease in her foetus.

It is well recognized that the variation in response to a given antigen between one subject and another may be very great. In the case of human subjects it is apparent that the formation of immune agglutinins against the Rh agglutinogen sometimes only occurs after repeated stimuli. This evidence has been gained from an analysis of cases in which an Rh negative person has received repeated transfusions of Rh positive blood before developing signs of incompatibility (see Wiener and Peters[21], Wiener[22]; Vogel, Rosenthal and Levine[23]). We have observed several cases in which an Rh negative person fails to form anti-Rh agglutinins after a first transfusion of Rh positive blood. Moreover, it can be demonstrated that the Rh positive erythrocytes survive normally (i.e. for 3 months or more) in the recipient's circulation. Such cases provide a rough parallel to those in which an Rh negative mother bears a first Rh positive child unaffected with haemolytic disease.

On the other hand, Dacie and Mollison[24] have reported a case in which an Rh negative woman responded to a first Rh positive transfusion by producing anti-Rh agglutinins. This woman had not received any previous transfusions and her only child was Rh negative. A parallel to this case is provided by those cases in which an Rh negative mother produces anti-Rh agglutinins in response to her first pregnancy (foetus Rh positive) and gives birth to an affected infant.

In contrast to the very variable response to stimulation by the Rh agglutinogen, the response to the A and B agglutinogens appears to be more regular. This may be because when an individual lacks the A or B agglutinogen his serum contains the corresponding anti-A or anti-B agglutinins, whereas the serum of an Rh negative person does not normally contain any anti-Rh agglutinins. In all the cases in which serial

titrations of iso-agglutinins has been made after an incompatible blood transfusion a response of the affected agglutinin has been observed. (Rø,[25] Zacho,[26] Wiener,[27] Lauer,[28] Wiener, et al, [6, 22, 29] Mollison and Young,[30] Krah[31]). There is also evidence that the injection of soluble antigen (as in Seitz-filtered plasma or serum) usually provokes an immune response. (Aubert, Boorman and Dodd[8]).

It is well known that a person who has become sensitized to a particular antigen is likely to respond to a subsequent stimulation by the same antigen. From the known facts of immunity it will be expected that some subjects will show a better response to the second or subsequent stimuli, whereas in others the response to the second or subsequent stimuli will be no better than that to the first stimulus and may even be worse. In fact in a series of cases in which the titre of anti-Rh agglutinins in the sera of mothers who have had only one affected infant has been compared with a series in which mothers have given birth to 2 or more affected infants, the titre of the agglutinins was on the average slightly higher in the former group (unpublished data).

As anti-A and anti-B iso-agglutinins very rarely cause any damage to the foetal erythrocytes even when present in exceptionally high titre, it is clear that in most cases there is much better protection against these than against anti-Rh agglutinins. This protection is probably due to the neutralization of the maternal antibodies by the soluble group-specific substances in the body fluids of the foetus before they enter the foetal circulation.

Thus, when a mother lacks an agglutinogen present in the erythrocytes of the foetus it seems that the most important factor determining whether that foetus will be affected with haemolytic disease is, in the case of an ABO incompatibility, the amount of group-specific substance in the foetal body fluids, and in the case of an Rh negative mother with an Rh positive foetus, her ability to form immune anti-Rh agglutinins.

Summary.

Results.

The results of serological tests in the various groups examined may be summarized as follows:

(1) *Cases of Haemolytic Disease of the Foetus in which the Diagnosis was established according to certain defined criteria.*

Of 100 mothers tested, 97 were Rh negative and 3 Rh positive. Sera of the Rh negative mothers contained anti-Rh agglutinins in 93 out of 97 instances. 79 affected infants of Rh negative mothers were tested; all were Rh positive. 45 husbands of Rh negative mothers tested were all Rh positive.

The sera of all three Rh positive mothers contained immune agglutinins incompatible with the foetal erythrocytes. In one instance the agglutinin was anti-Rh_2 and in the other 2 cases the agglutinin was anti-B.

(2) *Cases of Stillbirth or Neonatal death in which the Diagnosis of Haemolytic Disease was not established according to certain defined criteria.*

Seventy mothers were tested; 17 were Rh negative, 53 Rh positive. Anti-Rh agglutinins were found in the sera of 11 of the 17 Rh negative mothers. Amongst these 11 cases in which the mother's serum contained immune anti-Rh agglutinins, the foetus was stillborn during the last 3 months of pregnancy in almost every case. It is concluded that in these cases the foetal death was due to haemolytic disease. Very potent immune anti-A or anti-B agglutinins

were found in the sera of 3 of the 53 positive mothers. No definite opinion as to whether these infants were affected with haemolytic disease can be given.

In the remaining 56 cases, death of the foetus may have been due to haemolytic disease in a few instances since in any individual case serological tests cannot completely exclude this possibility in the present state of knowledge. The results of the tests in Section I, however, make it appear most unlikely that many cases in this group, taking it as a whole, were due to haemolytic disease. The majority of these cases were of early miscarriage, although in a few instances the foetus was stillborn at or near full-time and in at least one instance the diagnosis of hydrops foetalis was made on clinical grounds.

(3) *Families in which the Infant was Normal (in many instances affected with Physiological Jaundice).*

In testing a series of mothers and infants in cases in which the infant was thought to be merely affected with "physiological jaundice" it was observed that the mother's serum contained anti-Rh agglutinins in 3 cases out of 60; in these cases the infant was Rh positive, but in only one instance did close examination suggest that the infant might be mildly affected with haemolytic disease. In the two other instances the infant's blood picture remained strictly normal.

In the remaining 57 cases tests were made to see whether incompatibility between the mother's serum and the infant's erythrocytes (with regard to the anti-A and anti-B agglutinins) was correlated with the development of jaundice in the infant. It was found, however, that the incidence of incompatibility in this group was not significantly greater than in a random sample of mothers and infants. From this and other evidence it is concluded that in at least the majority of cases of "physiological jaundice" the development of the jaundice is not due to destruction of the foetal erythrocytes by immune agglutinins formed in the mother's serum. At the same time it is pointed out that mild cases of haemolytic disease of the newborn may sometimes be mistaken for cases of "physiological jaundice" unless serological tests are made.

Conclusions.

The Value of Serological Tests in Diagnosis.

When the infant is suspected of being affected with haemolytic disease, the finding in the mother's serum of immune atypical agglutinins (usually anti-Rh) can be accepted as almost conclusive evidence of affection. The finding of exceedingly potent anti-A or anti-B agglutinins may have the same significance, but this finding has to be interpreted in the light of experience.

Failure to find immune agglutinins in the mother's serum on the other hand does not exclude the diagnosis, particularly when the mother's serum is not examined until say more than 20 days after delivery.

The mere demonstration that the infant (or father) is Rh positive and the mother Rh negative can be considered no more than suggestive evidence of affection in the face of failure to find anti-Rh agglutinins in the mother's serum.

The demonstration that the mother is Rh positive clearly by no means excludes the diagnosis, although in these circumstances failure to find any immune atypical agglutinins, including varieties of anti-Rh, or to find very potent anti-A or anti-B agglutinins in her serum makes the diagnosis unlikely.

The value of serological tests in prognosis in families in which the occurrence

of haemolytic disease of the foetus is suspected, may be summarized as follows:

(1) When one or more unexplained stillbirths have occurred, the likelihood of their being caused by iso-immunization can be examined. Although the incrimination of iso-immunization as a cause will usually lead to the formation of a gloomy prognosis, this may at least save the patient from expensive and unnecessary treatment and should ensure that she does not suffer harm by receiving an Rh positive blood transfusion.

(2) In families in which one or more possible cases of haemolytic disease have occurred, some idea of the prognosis for future siblings can be gained by testing any living siblings, for if any of them is found to be Rh negative there will be an equal chance of an Rh negative and therefore normal child in any subsequent pregnancy.

These serological tests are likely to prove most helpful in (i) cases of stillbirth when the foetus is not or cannot be properly examined; (ii) in cases in which an infant is jaundiced but the diagnosis of haemolytic disease is in doubt; (iii) as a routine in women of child-bearing age (a) to detect Rh negative persons so as to ensure that they do not receive Rh positive transfusions; (b) to detect anti-Rh agglutinins in the sera of Rh negative women so that birth of an affected infant can be anticipated and steps taken to provide facilities for its early treatment with Rh negative blood transfusions.

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A Unique Constructive Operation

BY

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AND

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IN the autumn of 1942 a girl of eighteen was seen by one of us (V.B.) on account of monthly pain, which had been regularly recurring for over two years, though she had never menstruated. It was found that the vagina was absent and by rectal examination two tumours, each very laterally placed, were felt high up in the pelvis. As it was impossible to say whether the tumours represented a double uterus, two distended undeveloped horns, or two ovarian tumours, the abdomen was opened through a transverse incision in the pubic hair area. It was then ascertained that a double uterus was present, the body of each of which was about the size of a medium pear, but no cervix (vaginal or supravaginal) could be felt attached to either. A normal tube and ovary were appended to each uterus. The abdominal incision was then closed.

The patient was a particularly well-grown and pretty girl and it was determined to establish a vagina by McIndoe's indwelling graft technique and at the same time join the two uterine bodies and fashion a cervix. A month later therefore with the patient in the lithotomy position, a track was made between the rectum and the urethra and bladder, and a ring-forceps was pushed up to the top of it and held in place by packing with moist saline gauze. The transverse incision was then reopened and an anterior peritoneal flap turned back. To do this it was necessary to divide a median peritoneal fold joining the back of the bladder to the front of the rectum, and it was then found that each uterine body was continuous at its lower end with a sheet of tissue about $\frac{1}{4}$ inch thick which seemed to pass into the cardinal ligament on each side. Not only were no cervices present and the bodies very laterally placed, but they lay about $2\frac{1}{2}$ inches above the level of the bulge caused by the ring-forceps lying in the vaginal track which could be seen and felt distinctly (Fig. 1).

The inner side of each body was then incised and the cavities opened, when another disappointment was discovered, for though both of them contained a little menstrual blood, neither of them was distended, the size of the bodies being caused by the great thickness of their walls. The cavities ended blindly at the bottom of each body.

The sheet of tissue in which each body ended was then mesially split by scissors right down to the point where the top of the ring-forceps bulged and the tissue over it being divided, the top of the forceps was pushed through into the abdominal cavity (Fig. 2).

The inner side of each body having been trimmed for better suturing, the two back walls were joined to each other by interrupted catgut sutures with the knots on the back, and these sutures were continued downwards to unite the edges of the mesial split previously made in the sheet of tissue

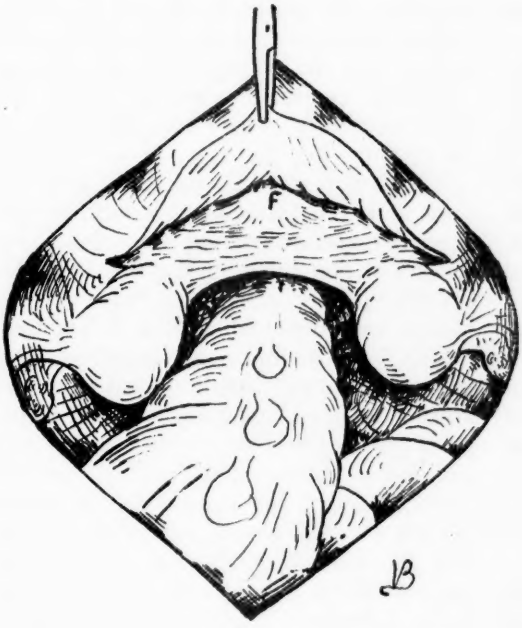

FIG. 1.

The peritoneal flap and bladder being reflected the sheet of tissue is seen in which the bodies of the uteri end. F marks the bulge caused by the ring forceps in the vaginal track.

FIG. 2.

The inner sides of the bodies are divided and the cavities exposed. The tissue sheet is split mesially and the top of the ring forceps is pushed through into the abdominal cavity.

with which the bodies were continuous (Fig. 3).

A piece of pressure tubing $\frac{1}{3}$ inch in diameter, covered with a split skin graft, raw surface outwards, like a cigarette paper, was then placed in the jaws of the ring-forceps and drawn down through the vaginal track till its lower end was just outside the vulva. (A large split skin graft, $8'' \times 3\frac{1}{2}''$, had already been cut freehand from the inner side of the left thigh in anticipation of the final stage of the operation, A.H.M.) The skin was fixed to the tube with mastisol in such a way that the upper $1\frac{1}{2}$ inch, which was to lie in the cavity of the reconstructed uterus, was uncovered. The next $2\frac{1}{2}$ inches was covered with skin where it was to lie in the constructed cervix, and the rest of it, which lay in the vaginal track, was left uncovered. (Fig. 4.)

The tube being placed in position, the fundus and anterior wall of the uterus on either side were joined together by interrupted sutures, knots outwards, and then the graft-covered portion of the tube was buried over by picking up the tissues of the sheet on either side by deeply inserted Lembert sutures of catgut (Fig. 5.) The bladder and peritoneal flap were then replaced and the round ligaments were pleated so as to keep the now single uterus forwards. The abdominal wound was then closed.

The patient was once more placed in the lithotomy position for the construction of the vagina (A.H.M.). A specially made mould, covered with the remainder of the split skin graft in one piece and fixed with mastisol, was inserted into the vaginal track which, by trial and error had been made just sufficiently large to accommodate it in comfort. The mould had a channel through the centre, through which passed the lower part of the pressure tubing inserted during the abdominal part of the operation. The mould was finally secured in position by incising the tissues round the vaginal introitus and suturing them with catgut and silk, leaving a hole through which the central tube emerged, and another anteriorly, which allowed access to the urethra (Fig. 6).

The patient stood the operation remarkably well. The abdominal wound healed normally and at no time were there any untoward abdominal symptoms. On the seventh post-operative day the vaginal mould was removed and a satisfactory "take" was found to have occurred. The pressure tube was also removed from the uterus, the cavity carefully irrigated and a short piece of de Pezzer catheter (No. 11) inserted so that the cut end lay towards the fundus and the expanded end snugly against the junction of the cervical canal and the vagina. Following this a glass vaginal dilator (No. 6) was put in and held by a T binder. This was removed once daily for vaginal irrigations of normal saline and weak dettol but at no time of the day or night was the dilator out for more than five minutes. The cervical tube was removed at the end of the fifth week. This programme was carried on until the 63rd day, at which time a small persistently raw area on the left vaginal vault was regrafted with a "postage-stamp" of split skin applied to the glass dilator. Healing rapidly occurred.

One hundred and nine days after the operation, the first undoubtedly discernible period occurred. It lasted for three days and was accompanied by slight premenstrual pain. Clots were passed. The next period took place fourteen days later and the third thirty-five days after the second. Thereafter the patient menstruated normally every twenty-eight days and has continued to do so up to the present time. Menstruation lasts two to three days, is preceded by mild pain and breast signs and is associated with moderate bleeding. It is

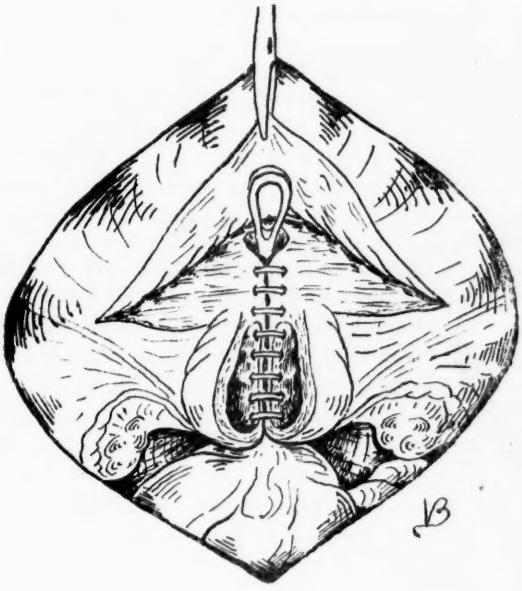

FIG. 3.

The posterior walls are united with sutures and the mesial split also sutured.

FIG. 4.

A length of pressure tubing is pulled down the vaginal track. Two and a half inches of it are covered with a skin graft. The upper one and a half inches is not covered as it is to lie in the uterus.

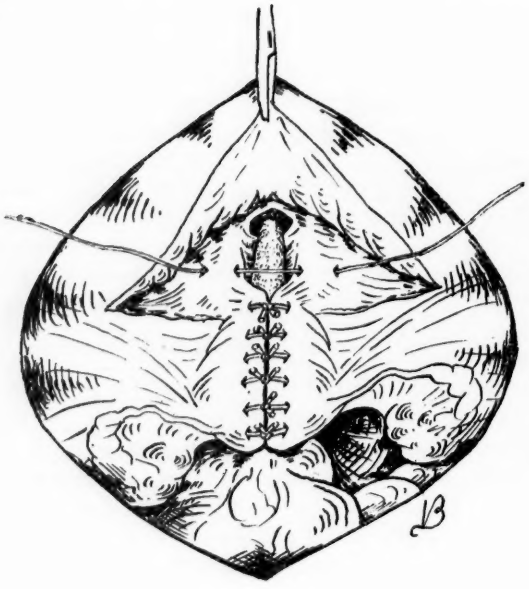

FIG. 5.

The anterior uterine walls are joined together and the graft-covered part of the tube is buried by overfolding the tissues of the sheet so as to form a cervix.

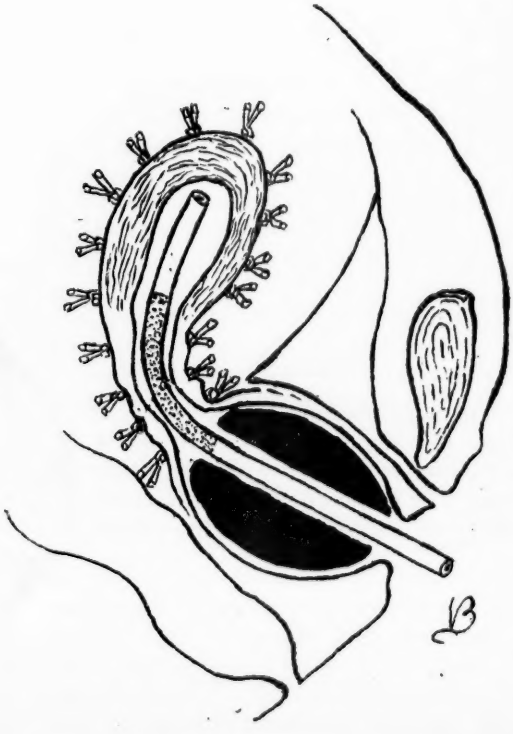

FIG. 6.

Diagram showing the uterus and the constructed cervix, with the position of the sutures: also the tube with its skin-covered section (dotted) and the position of the mould in the vaginal track.

now 14 months since the operation was performed. Continuous dilatation was carried out for six months, after which the glass mould was removed for gradually lengthening periods, and now it is worn for one night per week as a precaution against contraction. When she marries it can be discarded completely.

On examination the abdominal scar is sound and will soon become practically invisible. The vagina is ample in size and feels entirely normal except that instead of the normal vault and vaginal cervix, there is a funnel shaped extension which ends in the canal communicating with the body of the uterus. She is very well and doing war work. She will be able to marry if she wishes, and indeed is at the present moment engaged. She is certainly capable of becoming pregnant, though to what extent an artificial in place of a normal cervix will by reason of the absence of ciliated epithelium militate against it, is a matter which time alone can decide. If she does become pregnant, delivery will have to be by Caesarian section.

We have called the case a unique one, for nothing comparable to it has been described in the literature and it is almost certainly the first of its kind. Our united experience of congenital absence of the vagina amounts to about sixty cases. One of us (V.B.) has seen about thirty, of which he operated on seven by Baldwin's method. The other (A.H.M.) has operated on thirty cases by his own technique. In this conjoined series there were only two patients in whom a functioning uterus was associated with congenital absence of the vagina. The case herein described is one, and the other had a single functioning uterus which was succesfully united to a constructed vagina (A.H.M.) and now menstruates regularly and normally. The frequency of this rare combination is therefore not more than 4 per cent of the total number of cases of congenital absence of the vagina. The question how much rarer is congenital absence with a double functional uterus we leave to be answered by someone more versed in mathematics than we are.

In conclusion we hope we shall be forgiven if we stand back for a moment and as mere observers marvel at the advances surgery has made since we, and particularly the elder of us, entered upon the art. Even at the beginning of this century the possibility of cure in a case like this would have been regarded as the very shadow of a dream. There is little reason for believing that surgery has reached a static position or that further advancement is impossible. Doubtless there are large fields yet to explore and within them glorious opportunities for achievement.

The Placenta in Eclampsia and Nephritic Toxaemia

BY

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THIS communication is based on the study of over 100 toxaemic cases occurring in the Rotunda Hospital. The expenses of the investigation have been borne by the Irish Medical Research Council to whom the authors tender their thanks.

In a previous article published in March, 1942,[1] in the *Irish Journal of Medical Science*, the subject of placental infarcts in relationship to eclampsia and nephritic toxaemia was discussed and the work of James Young[2] and that of Bartholomew and Colvin[3] were cited and the importance of the contributions of these authors was brought to the attention of those interested in the problem of the aetiology of eclampsia.

The outlook on eclampsia so ably presented by Irving[4] in 1936, that the condition is a disease of all the arterioles, has rendered the treatment of the condition less empirical and the investigation of the pathology more fruitful.

The object of this paper is to show certain constant lesions of the placenta associated with eclampsia and to show, as Young[5] did in 1914, that these lesions are not very obvious to the superficial observer but that the acute nature of the lesions is a factor in rendering their recognition difficult.

Any area subjected to 'infarction' in the placenta may have been deprived of either the blood coming from the utero-placental arteries (maternal) or the blood coming through the foetal vessels.

The position and size of a large infarct most often corresponds to the cotyledon and as the cotyledon is a unit composed of a large branch of the villous tree surrounded by walls formed of placental septs and bathed by maternal blood entering through the basal limits of the placenta, interference with either foetal or maternal circulation might be equally effective in producing 'infarction.'

Although inclined to the opinion that the lesion is in the foetal blood supply, we have no evidence bearing on the problem other than that gross separation of the placenta is not a common accompaniment of infarction in eclampsia.

The lesions shown in cases of chronic nephritis complicated by pregnancy suggest strongly that some of the lesions described as infarcts are due to interference with the maternal blood supply.

By an infarct we mean an area of changed appearance in the placental substance which is obviously due to some major disturbance of either the foetal or maternal circulation.

By a study of sections of numerous placentae which have been fixed immediately after delivery it has been possible to recognize the various stages of infarct formation which may be briefly described as follows:

1st Stage. Extreme injection of large and small vessels of the villous tree right down to the terminal capillaries, associated with narrowing of the intervillous spaces.

2nd Stage. Obliteration of the intervillous spaces with commencing loss of definition of the structure of the villi. Foetal blood is still seen distending the vessels.

3rd Stage. The villi have lost their sharp staining characteristics and are lying together; the whole infarcted area is becoming homogenous in appearance. Gradually this condition leads on to an almost complete loss of structure.

The first and second stages of infarction may always be seen in conjunction with eclampsia and may be recognized, if the fresh placenta is examined critically, by the dark purple colour of the infarcted area.

The third stage of infarction is a constant finding in association with pregnancy complicating chronic nephritis and may also be found in patients who have developed eclampsia after a prolonged period of albuminuria (pre-eclampsia).

The following case histories with the photographs and descriptions of the placenta will demonstrate the association of the acute lesion with eclampsia and the chronic lesion with nephritic toxaemia. In addition the lesion associated with a retroplacental haematoma is shown in the latter condition with its effect on the adjacent placental tissue.

Case 1 (Plate I).

A.F. February 11th, 1942. Married female, age 27 years; housewife; 2-para.

Nephritic Toxaemia.

Pre-Retinitis. Classical Section.

Admitted at 13.50 hours, February 11th, 1942.

Complaint. Twenty-six weeks amenorrhoea; swelling of ankles; puffiness of eyelids; depression and insomnia—duration 7 days.

Present history. Patient received antenatal care from the 12th week of pregnancy. She was apparently normal until one week before admission when her complaint commenced.

Previous history. No serious illnesses. Her first pregnancy was uneventful until the 26th week when she complained of signs of toxaemia and suddenly developed toxaemic accidental haemorrhage. The baby was born dead.

General examination. On admission: pulse 82 per minute; temperature 98.8°F.; blood-pressure 156/100; urine, albumin trace.

General condition good; some evidence of anaemia; red-blood cells, 3,000,000; haemoglobin 60 per cent; slight oedema of ankles and hands; heart and chest normal.

Abdominal examination. Uterus size of 26 weeks pregnancy; vertex I presentation; head floating; F.H.H.

Progress and Treatment.

Patient placed on routine treatment for toxaemia; abundant fluids. Campolon 2 c.c. daily.

February 13th, 1942. Blood-pressure 160/100; albumin present; general condition unchanged. Examination of optic fundi showed signs of marked ' pre-retinitis '; no haemorrhage or exudates.

February 15th, 1942. General condition much the same. Blood-pressure 166/110; albumin present. Fluid intake restricted.

February 18th, 1942. Blood-pressure 180/120; albumin present; no change in optic fundi. Patient feeling reasonably well.

February 24th, 1942. Blood-pressure 200/120; albumin present; no other change in condition.

February 27th, 1942. Condition the same. Fluid intake and excretion good. Patient examined vaginally with a view of ascertaining more accurately the size of the baby and the state of the cervix. The cervix was long and thick; os was closed presenting part vertex. Baby estimated to be approximately 2 pounds weight.

February 28th, 1942. Blood-pressure 220/130; albumin abundant. In view of the steadily increasing blood-pressure and the increased albuminuria, it was considered advisable to deliver the patient immediately. On account of the small size of the baby Caesarean section was selected as the method of choice.

11.15 hours. Under gas, oxygen and ether anaesthesia a classical Caesarean section was performed. The peritoneal cavity contained a moderate quantity of free fluid. The patient was delivered of a live male child weighing 1 pound 15 ounces; the baby was in good condition.

The puerperium was uncomplicated and the

patient made a rapid recovery on her first day. Blood-pressure, 180/110; albumin present. Examination of the optic fundi still showed 'Preretinitis' condition to be present.

The baby died in 48 hours of prematurity. When the patient was discharged on her 18th day her blood-pressure was 160/100. Albumin nil.

On numerous occasions microscopy of urine showed many hyaline and granular casts as well as a few red-blood cells.

Case 2 (Plate II).

B.C. March 22nd, 1942. Unmarried female, age 18 years; primipara.

Ante-partum Eclampsia.

Admitted at 06.10 hours, March 22nd, 1942.

Complaint. Thirty-two weeks amenorrhoea; 2 epileptiform fits, the first 1 hour and the second 20 minutes before admission.

Present history. Patient was well until one week before admission when she noticed her ankles were swollen and her face tended to be puffy. Three days later she experienced constant headaches during the day.

Previous history. Nil.

General examination. On admission: pulse 104 per minute; temperature 97.0°F.; blood-pressure 140/100; urine, albumin present.

General condition poor; pulse volume not good; patient rather cyanosed. Moderate oedema of ankles, hands and face. Heart and chest normal.

Abdominal examination. Uterus the size of a full-term pregnancy; average size baby; vertex I; head fixed; F.H.H.; no evidence of uterine action.

Progress and Treatment.

March 22nd, 1942. Routine treatment for eclampsia instituted. Five minutes after admission the patient had third fit lasting one minute. Fifteen minutes later fourth fit lasting 3 minutes occurred. Marked cyanosis present. Patient unconscious for one hour after the fit.

14.30 hours. Fifth fit; no cyanosis; unconsciousness lasting 20 minutes; blood-pressure 168/120; albumin abundant.

18.30 hours. Sixth fit lasting one minute; cyanosis marked; unconsciousness lasting half an hour.

19.00 hours. Intramuscular Mag. Sulph. therapy repeated, lumbar puncture performed and 28 c.c. of clear cerebro spinal fluid, which was under considerable pressure were withdrawn. Two hours later the general condition of patient was much improved; no further fits and patient quite conscious; taking fluids freely.

March 23rd, 1942. Blood pressure 160/110; albumin abundant; fluid intake and excretion good; no further fits; patient quite conscious.

March 24th, 1942. Condition unchanged.

March 24th, 1942. Condition much better; patient almost back to normal. Blood-pressure 134/90; albumin trace.

04.00 hours. Good labour pains commenced and 7 hours later patient delivered herself spontaneously of a live female child weighing 7 pounds 8 ounces.

The patient made a rapid recovery and the puerperium was uneventful. On the second day blood-pressure 128/86; albumin nil; and when discharged on the 10th day blood-pressure and urine were down to normal.

Microscopy of urine on the day after admission showed many blood cells and no casts.

Case 3 (Plate III).

M.K. March 29th, 1942. Unmarried female, age 28 years; primipara.

Ante- and Intra-partum Eclampsia. Retinal Detachment. Tent Induction. Spontaneous Delivery. Mors.

Admitted at 10.00 hours, March 29th, 1942.

Complaint. Thirty-two weeks amenorrhoea complicated by fits—duration 6 hours.

Present history. Patient was apparently well 6 hours before admission when she had an eclamptic fit. Two more fits occurred within the next 3 hours; the patient was then seen by a doctor who gave her morphia, grs. ¼ and sent her into hospital.

Previous history. Nil.

General examination. On admission: Pulse 80 per minute; temperature 98.0°F.; blood-pressure 170/112; urine, albumin abundant.

Patient conscious but mentally confused; general condition fair; the tongue was bruised and oedematous; no oedema of ankles; heart and chest normal.

Abdominal examination. Uterus size of 34 weeks pregnancy; vertex presentation; F.H.H.; uterine contractions not palpable.

PROGRESS AND TREATMENT.

The routine treatment for eclampsia was fully carried out. The Mist. Senna Co. given by mouth was immediately vomited. The enema was partly retained.

March 29th, 1942. 11.45 hours. Patient had fourth fit followed by unconsciousness lasting half hour. Two hours later patient was perfectly conscious and talking rationally.

March 30th, 1942. No more fits; patient taking fluids very well; completely conscious; blood-pressure 176/90; albumin abundant.

For the following 3 days patient's condition remained more or less stationary but her blood-pressure appeared to be steadily rising.

April 3rd, 1942. Her general condition apparently improved; fluid intake good; excretion good; blood-pressure 200/120; albumin abundant. Patient complaining of severe headaches and dimness of vision.

April 4th, 1942. Condition unchanged; blood-pressure 200/130; albumin abundant. Examination of optic fundi showed that on the right side there was some central oedema; no local haemorrhage or exudates; there was a shallow detachment of the retina below; on the left side there was one local area of haemorrhage on the superior temporal vessel and a large round detachment below.

On account of the apparent deterioration of the patient's condition it was then decided to induce labour. On vaginal examination the cervix was long and thick and the os closed. Tents 4 and 1 gauze pack inserted.

April 5th, 1942. Condition unchanged; blood-pressure 212/140; albumin abundant. The fundi showed no fresh changes with the exception of some increase in the areas of detachment; no uterine pains; the Tents and gauze pack were removed; the os was 2 fingers and through this the membranes were punctured; F.H.N.H.; 8 hours later small labour pains commenced.

April 6th, 1942. Labour pains continuing and improving.

04.00 hours. Complaining of very severe headache; extremely restless and rather irritable; temperature 103.8°F.; pulse 120; morphia grs. ¼.

06.30 hours. Condition unchanged; blood-pressure 212/140; albumin abundant. Lumbar puncture performed; cerebro-spinal fluid under slight tension; clear; 8 c.c. removed.

07.00 hours. Pulse 80 per minute; temperature 98.2°F. Patient much improved; less restless; not complaining of headache and tending to go to sleep.

10.00 hours. Labour continuing and pains improving; patient conscious and taking fluids freely; no headache; blood-pressure 180/130.

15.15 hours. Patient had fifth fit; not severe and unattended by cyanosis; unconscious for 10 minutes only, and thereafter condition appeared to be good. Uterine contractions were much stronger. Morphia grs. ¼ and Mag. Sulph. 20 per cent intramuscularly; lumbar puncture performed, 15 c.c. of clear fluid withdrawn under slight tension; patient given 1 pint of 20 per cent glucose intravenously.

17.55 hours. Spontaneous delivery of dead foetus weighing 3 pounds 6 ounces; placenta was delivered in 10 minutes and it contained numerous large recent infarcts. Condition improved thereafter and patient inclined to sleep normally; fluid intake good; excretion tending to diminish.

April 7th, 1942. Blood-pressure 160/115; albumin present. Conscious and taking fluids freely. Excretion still poor—8 ounces during previous 24 hours. Patient given 1 pint of 5 per cent glucose in normal saline intravenously

17.00 hours. Patient constantly complaining of very severe headache and becoming restless; half hour later pulse became very rapid and thready; patient stopped breathing and died.

Analysis of urine showed numerous hyaline and granular casts with much blood.

CASE 4 (PLATE IV).

M.F. February 17th, 1942. Married female, age 28 years; housewife; 7-para.

CHRONIC NEPHRITIS. DEAD FOETUS.
TENT INDUCTION. MEMBRANES PUNCTURED.

Admitted at 10.30 hours, February 17th, 1942.

Complaint. None; pregnancy of 22 weeks duration.

Present history. Patient attended antenatal department on one occasion and was admitted immediately on account of hyperpiesia. She did not complain of headache or any other symptom of toxaemia.

Previous history. 1st, 2nd, 4th pregnancies were normal; 3rd and 5th pregnancies were premature

born dead; 6th pregnancy was an abortion. No history of previous illness.

General examination. On admission: Pulse 86 per minute; temperature 98.4°F.; blood-pressure 240/140; urine, albumin nil.

Condition fair; no anaemia; no oedema of ankles; heart and chest normal.

Abdominal examination. Uterus the size of a 20 weeks pregnancy; presentation doubtful; F.H.H.

PROGRESS AND TREATMENT.

Patient treated in routine manner. After 10 days blood-pressure 190/140; albumin nil. Patient felt well and insisted on being discharged on her own responsibility.

April 9th, 1942. Patient readmitted complaining of having felt no life for one month. Blood-pressure 240/140; albumin abundant.

Abdomen. Uterus size of 24 weeks pregnancy; F.H.N.H.; presentation doubtful.

The diagnosis of dead foetus was made and induction by means of tents was decided upon.

April 13th, 1942. *Per vaginam* os one finger; foetal parts not palpable. Tents 4 inserted and vaginal pack. No pains followed. 48 hours later tents and pack removed; os 3 fingers; membranes intact; collapsed foetal head palpable. Membranes were punctured and a moderate amount of meconium-stained liquor came away. Within 24 hours patient commenced labour and after one hour delivered herself spontaneously of a macerated foetus weighing 2 pounds 2 ounces.

The patient was apparently well during her puerperium; albuminuria cleared up completely on the first day but blood-pressure remained unchanged. Patient was discharged on her 10th day. Blood-pressure 230/140; albumin nil.

Microscopy of urine showed many hyaline and granular casts as well as much blood.

CASE 5 (PLATE V).

M.B. December 5th, 1941. Married female, age 29 years, housewife; primipara.

ALBUMINURIA.
PUNCTURE OF MEMBRANES.
POSTPARTUM ECLAMPSIA.

Admitted at 18.00 hours, December 5th, 1941.

Complaint. Swelling of the ankles—duration 3 weeks.

Present history. Admitted from the country, pregnant 38 weeks with swelling of the ankles of 3 weeks duration; no headaches; no visual phenomena.

Previous history. No previous illnesses.

General examination. On admission: Pulse 80 per minute; temperature 97.6°F.; blood-pressure 210/140; urine, albumin abundant.

General condition was good; there was marked oedema of the ankles extending up to the middle of the legs; none of the hands or face; heart and chest were normal.

Abdominal examination. Uterus enlarged to size of 38 weeks pregnancy; small baby; vertex I presentation; head freely mobile, but would push well into the brim.

PROGRESS AND TREATMENT.

Patient placed on the routine treatment for albuminuria. Response was moderately good; after 3 days blood-pressure 196/110; albumin trace. After 6 days blood-pressure 180/108; albumin present. Oedema much less marked. As albuminuria was recurring and patient only a week from term, induction of labour decided upon.

December 11th, 1941. 05.00 hours. Medicinal induction—excluding quinine but including Pitocin in ¼ c.c. doses—commenced.

11.00 hours. *Per vaginam.* Os one finger; cervix thinned out; low puncture of membranes and moderate amount of liquor drained away.

17.00 hours. Good labour pains commenced; head went down rapidly.

21.40 hours. Spontaneous delivery, living female child, weight 4 pounds 3 ounces. Third stage normal; placenta delivered in 30 minutes.

22.15 hours. Five minutes after delivery of placenta, patient had an eclamptic fit of short duration; conscious immediately afterwards. Albumin abundant. Routine treatment for eclampsia instituted; patient quite conscious and taking fluids freely.

December 12th, 1941. 08.00 hours. Patient had second fit lasting half a minute; unconscious for half an hour; blood-pressure 158/120; albumin abundant. Marked subconjunctival oedema present. Examination of fundi revealed lower half of each retina to be detached. Patient quite conscious and taking fluids freely.

December 14th, 1941. General condition much the same. Blood-pressure 160/120; albumin

abundant. Fluid intake and excretion both good. Retinoscopy showed detachment on right side to have disappeared completely, leaving a vertical "grey area" outside the macula. On left side detachment less; local retinal detachment down and out only. No conjunctival oedema was present.

December 16th, 1941. General condition unchanged. Blood-pressure 150/100; albumin abundant. Retinoscopy showed very small detachment close to macula in each fundus.

December 18th, 1941. General condition improved; blood-pressure 142/98; albumin nil. Remainder of puerperium uneventful; on discharge on 15th day, patient well. Blood-pressure 140/90; albumin nil. Baby sent to nursery at birth and improved rapidly. Discharged on its 37th day weighing 6 pounds 13 ounces.

Case 6 (Plate VI).

M.H. February 25th, 1942. Married female, age 20 years, housewife; primipara.

Eclampsia.

Spontaneous Delivery.

Admitted at 03.00 hours, February 25th, 1942.

Complaint. Several fits.

Present history. Admitted with a history of 36 weeks amenorrhoea having had 3 epileptiform fits. She had complained of headaches and swelling of the ankles for 2 days previously. The first fit was 3 hours before admission and the last fit 1 hour before admission.

Previous history. Nil.

General examination. On admission: Pulse 120 per minute; temperature 99.0°F.; blood-pressure 156/120; urine, albumin abundant.

General condition fair; patient conscious and taking fluids. Slight oedema of ankles. Colour good. Volume of pulse good. Heart and chest normal.

Abdominal examination. Uterus enlarged to size of 36 weeks pregnancy; average size baby; vertex I presentation; head fixed; F.H.H.

Progress and Treatment.

February 25th, 1942. 00.30 hours. Routine treatment for eclampsia instituted.

03.40 hours. Patient had fourth fit lasting one minute. Unconscious for 20 minutes afterwards but thereafter quite lucid and taking fluids by mouth.

08.00 hours. Fifth fit; conscious 20 minutes later.

11.30 hours. Sixth fit; conscious in 15 minutes. General condition much improved; fluid intake and excretion good. Blood-pressure 150/110; albumin present.

February 26th, 1942. Condition much the same; blood-pressure 180/130; albumin trace.

February 27th, 1942. 02.00 hours. Spontaneous onset of labour; pains moderately good; blood-pressure 190/120; albumin trace.

February 28th, 1942. 05.55 hours. Spontaneous delivery of a male child weighing 6 pounds 3 ounces. Blood-pressure 200/140; albumin abundant.

Puerperium complicated by streptococcal septicaemia. Cervical and throat swabs were positive for haemolytic streptococci. Pyrexia commenced on the 3rd morning. Temperature 103.6°F.; pulse 140 per minute; temperature and pulse maintained for 2 days; sudden fall by crisis to normal. Soluseptasine therapy in continuous drip saline 2 grammes per day. Proseptasine 4 grammes daily per mouth. On 5th evening temperature 101; pulse 110; fell by lysis. On 8th evening temperature and pulse normal. Puerperium thereafter uneventful. On discharge blood-pressure 140/95. Albumin nil.

With the exception of a few hyaline casts on the day of admission microscopy of urine showed no abnormalities.

Case 7 (Plate VII).

G.K. March 14th 1942. Married female, age 25 years; housewife: primipara.

Antepartum Eclampsia.

Spontaneous Delivery.

Admitted at 03.15 hours, March 14th, 1942.

Complaint. Two fits.

Present history. Forty weeks amenorrhoea; 2 epileptiform fits one hour before admission. The patient had been apparently well up to this time.

Previous history. No history of illness. Early in pregnancy was suffering from hyperemesis gravidarum; was found to have a retroverted uterus which was corrected. Remainder of pregnancy uncomplicated.

General examination. On admission: Pulse 88 per minute; temperature 97.6°F.; blood-pressure 165/120; urine, albumin abundant.

General condition good; slight oedema of ankles; heart and chest normal.

Abdominal examination. Uterus 3 fingers below xiphoid process; average size baby; vertex II presentation; head well engaged; F.H.H. No evidence of uterine activity.

PROGRESS AND TREATMENT.

March 14th, 1942. Routine treatment for eclampsia instituted. Fluid intake poor on account of constant vomiting; excretion poor—6 ounces in the first 24 hours.

March 15th, 1942. Condition much improved; blood-pressure 154/100; albumin trace. Fluid intake good; excretion good—24 ounces in 24 hours; no vomiting.

March 16th, 1942. 20.00 hours. Labour pains commenced. Blood-pressure 150/100; albumin abundant; no oedema; occasional vomiting. Pains were poor and head went down slowly.

March 17th, 1942. Blood-pressure 156/104; albumin abundant; labour pains continued during the day and were still inefficient. Patient complained of headache; occasional vomiting.

March 18th, 1942. 10.00 hours. Spontaneous delivery of live male child weighing 7 pounds. The placenta was delivered in 20 minutes and the 3rd stage was normal.

The patient made a rapid recovery. On her first day blood-pressure 146/96; albumin trace; fluid intake and excretion normal. The next day the urine was albumin free. The puerperium was uncomplicated and the patient was discharged on her 10th day. Blood-pressure 128/90; albumin nil.

The baby did well and was discharged with the mother.

CASE 8 (PLATE VIII).

P.G. December 20th, 1941. Married female, age 19 years; housewife; primipara.

CHRONIC NEPHRITIS.

Admitted at 17.30 hours, December 20th, 1941.

Complaint. Sent in from antenatal department feeling well.

Present history. Patient first attended antenatal department when 24 weeks pregnant. Blood-pressure 156/90; albumin nil. Given advice with regard to diet and rest. Three weeks later, blood-pressure 158-92; albumin nil. After a further 3 weeks, blood-pressure 164/100; albumin trace. Following day, December 20th, blood-pressure 164/110; albumin present. Patient admitted.

Previous history. No previous illnesses.

General examination. On admission; Pulse 88 per minute; temperature 98.4°F.; blood-pressure 164/110; urine, albumin trace.

Condition good; no oedema of face, hands or ankles. Heart and chest were normal.

Abdominal examination. Uterus size of 30 weeks pregnancy; vertex I, F.H.H.

PROGRESS AND TREATMENT.

Patient placed on routine treatment for albuminuria; very little response. After 4 days, blood-pressure 150/90; albumin present. Patient then went home on her own responsibility.

January 24th, 1942. Patient readmitted, blood-pressure 160/100; albumin present; no oedema. patient had had 36 weeks amenorrhoea at this stage. Uterus the size of 34 weeks pregnancy; vertex I; F.H.N.H. Routine treatment.

January 27th, 1942. Patient commenced labour. Blood-pressure 160/110; albumin nil. Within 2 hours spontaneous delivery of macerated foetus; placenta followed almost immediately.

Puerperium uneventful; no further albuminuria; blood-pressure remained stationary and on discharge on 10th day was 160/110.

CASE 9 (PLATE IX).

K.D. March 10th, 1942. Married female, age 27 years; housewife; 2-para.

CHRONIC NEPHRITIS.

CLASSICAL CAESAREAN SECTION.

Admitted at 18.00 hours, March 10th, 1942.

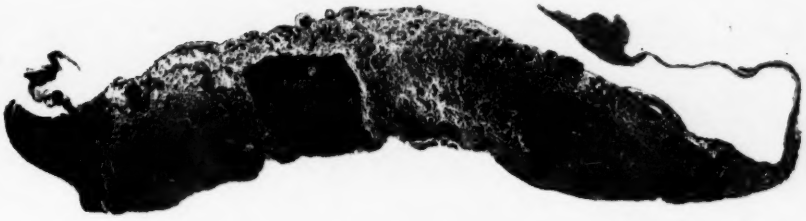
Complaint. Pregnancy of 33 weeks with marked swelling of the ankles of 4 days duration.

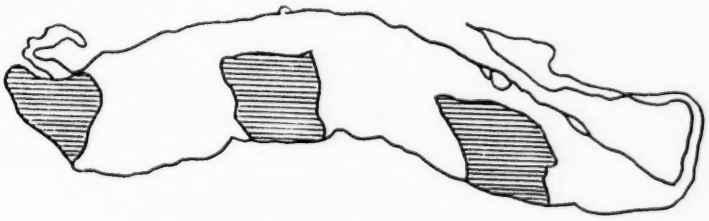
Present history. Patient received antenatal care from the 20th week of pregnancy. She was then well and blood-pressure 160/120; albumin nil. She felt quite well and her condition remained stationary up to the 30th week. She then complained of occasional headaches and blood-pressure 176/130; albumin nil; no oedema. Three weeks later she had marked oedema; no headaches; no eye signs; no epigastric pains; blood-pressure 190/140. Patient admitted immediately.

Previous history. First pregnancy, admitted to hospital at 33 weeks; blood-pressure 180/100; albumin abundant; F.H.H. Twenty-four hours later F.H. failed and medicinal induction was successful at the 5th attempt; 15 days later she delivered herself spontaneously of a dead male

Plate I

Case 1. Chronic Nephritic Placenta, No. 1.





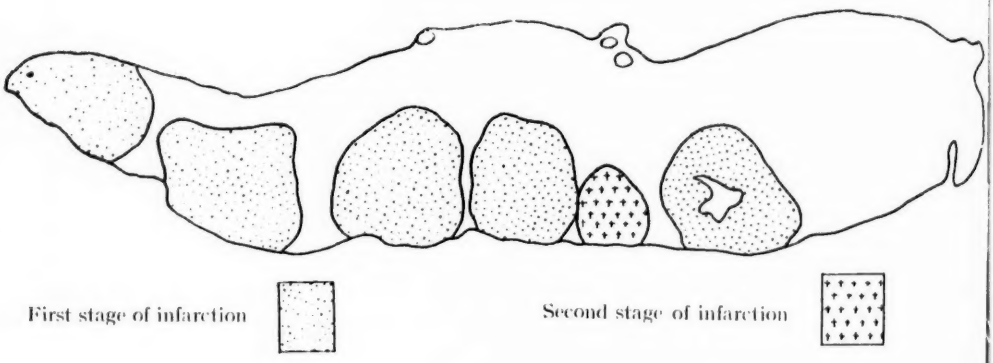
Third stage of infarction

This placenta shows involvement with large chronic infarcts. Three of these are distinctly shown in the section. Inspection of the remainder of the placenta shows functioning tissue illustrated by a normal intervillous space. The loss of definition in the infarcted areas suggests that the condition had existed many days preceding delivery.

The patient exhibited her first symptom at the 25th week—24 days before delivery. She was delivered by classical Caesarean section at the 29th week; the baby was alive. On admission the blood-pressure was 156/100 and on discharge was 160/100.

Plate II

Case 2. Eclamptic Placenta, No. 1.

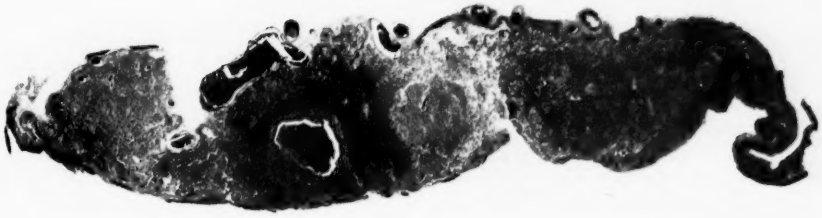


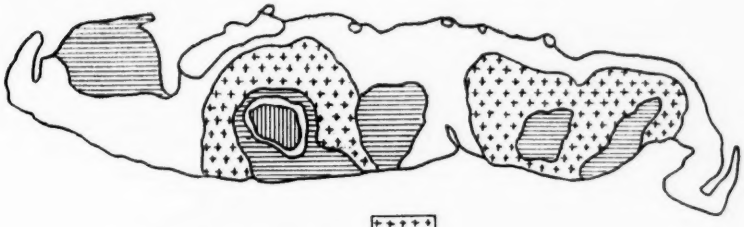
A general view of the placenta under a 1-inch objective shows apparently functioning placental tissue in so far as the intervillous spaces are well defined. All through the placenta the vessels of the villous tree are markedly hyperaemic. This, in the authors' opinion, is the earliest stage of infarction. These areas are demonstrated in the key diagram. In the centre of the picture is one area where the infarction is definitely established.

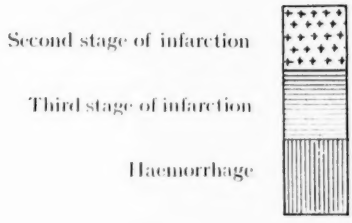
This patient had 6 fits over a period lasting 13 hours; the last fit occurred 3 days before delivery. The baby was alive.

Plate III

Case 3. Eclamptic Placenta, No. 5.





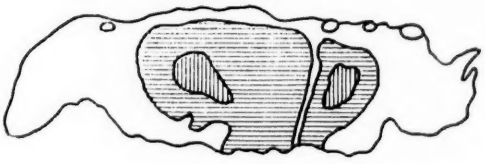


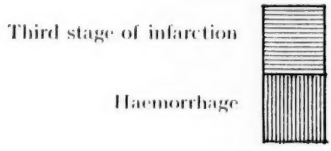
The general view shows very little normal placental tissue. A great part of the placenta is occupied by old infarcts. In the centre of one of these is an area occupied by old blood. The tissue surrounding this latter infarct, shows both extreme hyperaemia and obliteration of the intervillous space and may be regarded as an acute infarction of some days standing, but definitely more recent than the 5 areas described as being chronic. Two other similar areas are indicated which show very great congestion but less obliteration of the intervillous space and may be regarded as even more acute infarcts.

This patient had 5 fits, the first 4 of which occurred within 7 hours; there was an interval of 7 days before the last fit. The foetal heart failed 24 hours before delivery.

Plate IV

Case 4. Chronic Nephritic Placenta, No. 2.



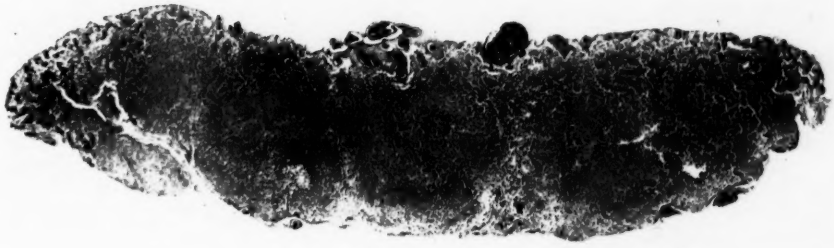


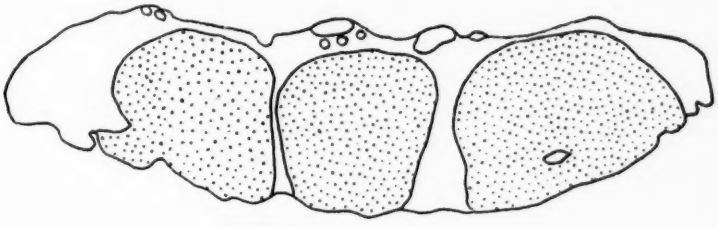
This placenta shows a very large area involved by chronic infarction. Only a small amount of normal placental tissue is present. The infarction is so chronic that it is difficult to say whether 2 or 3 cotyledons are involved. Gross intraplacental haemorrhages are present and their positions and the extent of the infarcts are shown in the key diagram.

The patient exhibited her first symptom at the 22nd week—7 weeks before delivery and some weeks before the death of the foetus. She was delivered spontaneously at the 29th week, after a tent induction; the baby was macerated. On admission the blood-pressure was 240/140 and on discharge was 230/140.

PLATE V

CASE 5. ECLAMPTIC PLACENTA, NO. 2.





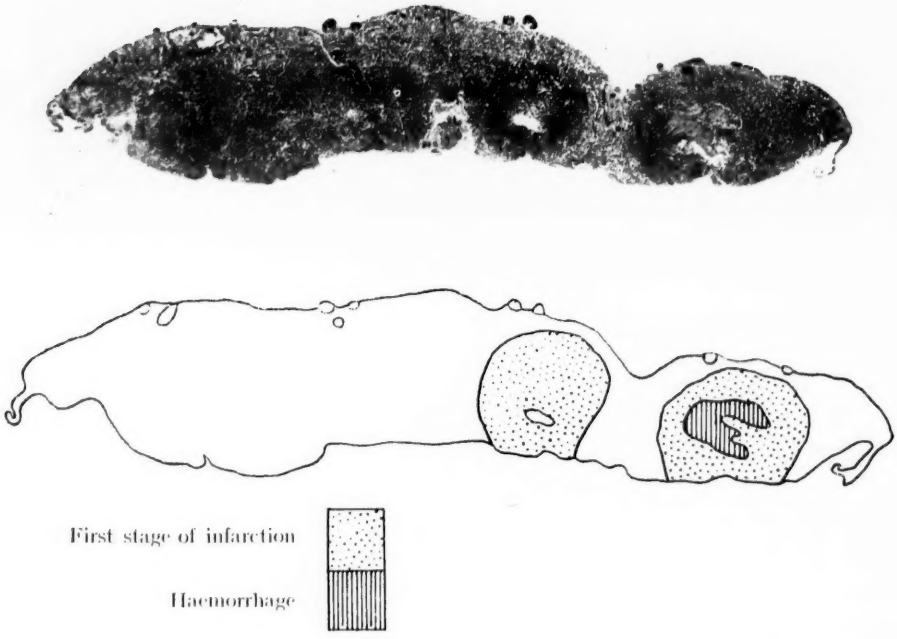
First stage of infarction

A general view of the placenta shows very marked hyperaemia which involves the whole placenta; these areas are outlined in the key diagram. In these areas the hyperaemia is most marked; while the intervillous space still exists, it is very restricted in many areas.

This patient had 2 fits—the first 35 minutes and the second 10½ hours after delivery. The baby was alive.

Plate VI

Case 6. Eclamptic Placenta, No. 3.

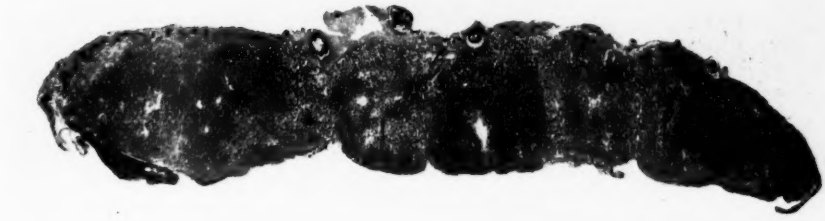


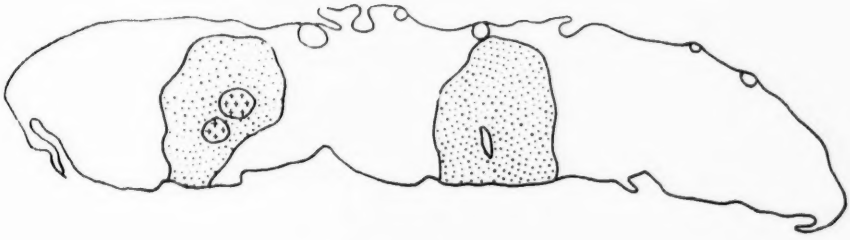
The whole placenta shows hyperaemia of the villous tree. Crowding of the villi with reduction of the intervillous space characterizes the whole placenta. In the two areas indicated on the key, hyperaemia is most marked and the intervillous space is almost obliterated. In one of these areas there is an intraplacental haemorrhage.

This patient had 6 fits over a period lasting 12 hours; the last fit occurred 3 days before delivery. The baby was alive.

PLATE VII

CASE 7. ECLAMPTIC PLACENTA, NO. 4.





First stage of infarction

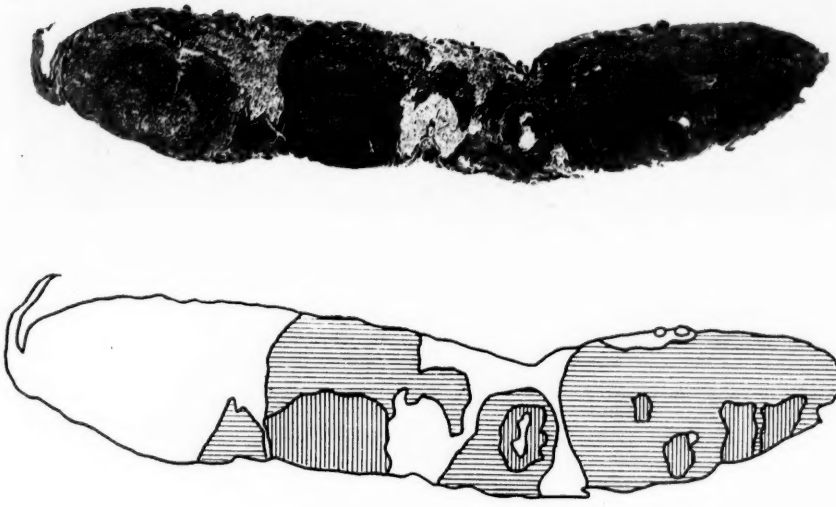
Second stage of infarction

The whole placenta shows marked injection of the villous tree, not only the larger trunks, but also the terminal vessels. A careful examination shows that the intervillous space is still practically normal. However, there are two areas marked in the key, which show marked injection of the vessels and small areas where the intervillous space has been obliterated. This may be regarded as an acute infarct passing from the stage of acute engorgement to necrosis.

This patient had 2 fits within half an hour; the last fit occurred four days before delivery. The baby was alive.

Plate VIII

Case 8. Chronic Nephritic Placenta, No. 4.

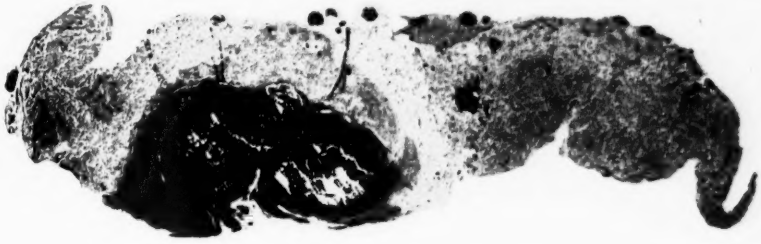


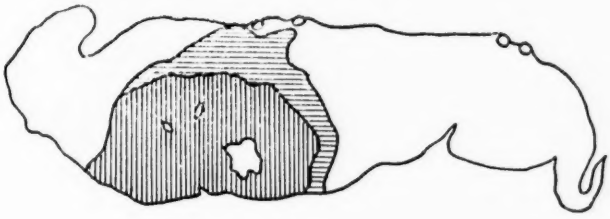
This placenta shows large areas of chronic infarction associated with several intraplacental haemorrhages and one large haemorrhage apparently retroplacental. The areas involved by infarction here, show very marked loss of the intervillous space as well as degenerative changes in the villi themselves. The remainder of the placenta appears to be functioning tissue.

The patient exhibited her first symptom at the 25th week—10 weeks before delivery. She was delivered spontaneously of a macerated foetus at the 34th week. On admission the blood-pressure was 164/110 and on discharge was 160/110.

Plate IX

Case 9. Chronic Nephritic Placenta, No. 3.





Third stage of infarction

Haemorrhage

A general examination of this placenta shows a large proportion of the placental tissue to be normal. In addition, a considerable area has been detached from the uterine wall by a haemorrhage. The adjacent tissue has undergone degenerative changes characterized by the loss of the intervillous space and by the homogenous appearance of the villi. This type of infarct would undoubtedly be due to the loss of maternal blood supply.

The patient exhibited her first symptom at the 20th week—13 weeks before delivery. She was delivered by classical Caesarean section at the 33rd week. The baby was alive. On admission the blood pressure was 204/140 and on discharge was 160/110.

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child weighing 2 pounds 11 ounces. No history of scarlet or rheumatic fevers or other serious illness.

General examination. On admission: Pulse 88 per minute; temperature 98.0°F.; blood-pressure 204/140; urine, albumin abundant.

General condition good; no evidence of anaemia; marked oedema of ankles; heart and chest normal.

Abdominal examination. Uterus the size of a 32 weeks pregnancy; vertex II presentation; F.H. good; baby approximately 3 pounds 8 ounces.

PROGRESS AND TREATMENT.

Condition remained stationary for the following 3 days; blood-pressure and albuminuria unchanged. Examination of optic fundi showed no retinitis but definite arterial constrictions were present.

March 13th, 1942. On account of the lack of response to the routine treatment of diet and abundant fluids and as the baby was considered viable, it was considered imperative that the patient should be delivered as soon as possible. Her previous history suggested that the placenta would be infarcted to a considerable extent. It was considered inadvisable to treat her by induction of labour and a classical Caesarean section was performed and the patient delivered of a living female child weighing 3 pounds 10 ounces.

Two days after delivery patient's general condition improved; blood-pressure 180/120; albumin present. The puerperium was uncomplicated and on the 14th day patient was discharged well. Blood-pressure 160/110; albumin nil. The baby did well for 10 days; then developed gastro-enteritis and died 14 days old.

Microscopy of the urine showed no casts of any description and with the exception of albuminuria was normal.

CONCLUSIONS

(1) Eclampsia is associated with a typical placental lesion of an acute form characterized by engorgement of the foetal circulation and a gradual disappearance of the intervillous space which means the disappearance of the maternal circulation and corresponding necrosis in the villous tree.

(2) One of the lesions in the placenta associated with nephritic toxaemia is a less acute condition of the same type. The reason for this is that the individual lesion may develop more slowly or that the placenta gradually becomes involved, cotyledon by cotyledon, whereas in eclampsia the whole placenta becomes involved suddenly. A second type of lesion is seen in nephritic toxaemia which is apparently directly due to partial placental separation with consequent degenerative change in the involved cotyledon.

(3) That the early stages in the lesion associated with eclampsia will still permit of the maintenance of function in so far as oxygenation of the foetus is concerned.

The question of imparting an aetiological importance to these acute lesions of the placenta should be approached with caution. Bartholomew has discussed the question very fully. Young's[6] recent work on accidental haemorrhage seems to bring the probability of the existence of placental toxins nearer to certainty.

We will allude only to one possible result of placental damage associated with the eclamptic lesion. In studying sections we have at times been doubtful as to whether foetal blood has been extravasated into the intervillous space. Should this be the case there may be forthcoming an explanation for the occurrence of eclampsia which would be comparable to the recent explanation of the occurrence of erythroblastosis foetalis.

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Two Unusual Causes of Intraperitoneal Bleeding Giving Rise to Collapse

BY

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WITHIN 2 months 2 cases profoundly collapsed by intra-peritoneal haemorrhage, were admitted under my care to the Royal Infirmary, Edinburgh. Both were wrongly diagnosed as ruptured extra-uterine gestations, but as the true causes of the collapse were much more rare and in the latter case possibly unique, it was thought that it might be of interest to put their histories on record.

CASE 1.

Perforation of advanced chorionepithelioma causing severe intra-peritoneal bleeding.

Mrs. Y., age 31 years, had had 3 pregnancies ending in a normal full-time delivery in 1935, a 7 months premature labour in 1937, after which the baby only lived a few days, and an abortion in September 1940, which was septic and probably criminally induced. Since that date her menstrual history was very irregular and there were reasons to make one suppose that she had had another abortion though she would not admit to it. Following the abortion in 1940 she had 6 months amenorrhoea, after which periods returned but were very scanty. Later she had floodings lasting 3 weeks at times, but at other times the loss was very scanty. (The patient was a most unreliable witness and though the utmost pains were taken to get a reliable history from her regarding her menstrual functions and abortions, she was very vague and each time a slightly different story was produced). From July 1942 until the beginning of October she had amenorrhea and this was followed by bleeding for 3 weeks. For 10 days she had been under her doctor's care for haemoptysis associated with some dullness at the base of the left lung. The doctor suspected a tubercular lesion but the sputum was found to be negative. On October 26th the patient was admitted as an emergency to my ward as she had been seized with sudden severe abdominal pain followed by collapse. Later she suffered from pain over her right shoulder. On admission the pulse was soft and running about 140 beats per minute, the temperature subnormal and the blood-pressure 70/– mm. Hg. She was very collapsed. Examination of her abdomen showed slight distension and definite tenderness all over; shifting dullness was present; on vaginal examination there was only slight bleeding, the cervix was closed and firm, the uterus was slightly enlarged, soft and anteverted and she was infinitely tender on palpation of the pouch of Douglas through the posterior fornix, this being especially noticeable on the left side. No definite mass was felt, but a fairly confident diagnosis of a ruptured extra-uterine gestation was made and immediate laparotomy was decided upon during which she was given a blood transfusion.

FIG. 1.
Coronal section of uterine body showing chorionepitheliomatous invasion of fundus and perforation at left cornu.

FIG. 2.
Muscular wall of the uterine fundus showing invasion by irregular masses of syncitium and Langhans's cells.

Magnification × 130.

FIG. 3.
Point of rupture of uterine cornu showing irregular mass of syncitium and Langhans's cells and blood clot.

Magnification × 130.

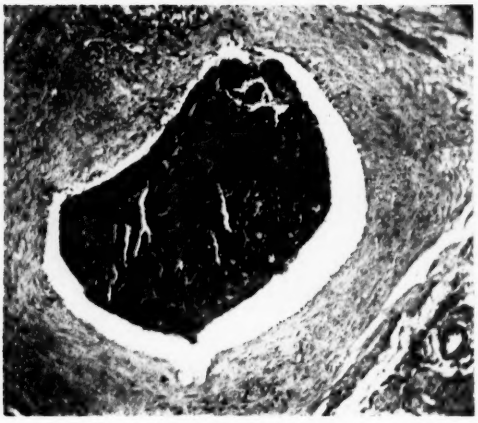

FIG. 4.

Blood vessel at uterine isthmus containing a plug of chorionepitheliomatous tissue.
Magnification × 50.

FIG. 5.

Chorionic villus showing proliferation of the trophoblast, hydropic degeneration of the stroma and few blood vessels.
Magnification × 50.

On opening the abdomen the peritoneal cavity was found to be full of blood and blood clot; both Fallopian tubes and ovaries were found to be healthy and there was not any evidence of tubal gestation. On examination of the body of the uterus, however, it was found to be enlarged to the size of a 6 to 8 weeks gestation and 2 haemorrhagic areas were found near the fundus anteriorly, one of which was bleeding profusely; these looked like perforations but it was impossible to say from what cause. As the openings were irregular it was not thought that sutures would be of any avail and as the patient was so collapsed and the possibility of a chorionepithelioma flashed through one's mind, it was decided to perform a hysterectomy. On pushing the bladder off the cervix another small opening was detected in the anterior wall of the cervix which, however, was not haemorrhagic and looked like an old standing perforation, possibly made at the time of her septic abortion in 1940. The cervix was amputated below this level and a certain amount of parametrial tissue, which was haemorrhagic, was removed with the cervix. The usual ligatures were applied, peritonising done, blood and blood clot removed as much as possible and the abdomen sutured quickly, the whole operation taking about 30 minutes; with the concurrent transfusion the condition of the patient was better at the end of the operation than it had been at the beginning.

As a criminal abortion was suspected the uterus was hardened before it was opened, when it was found that the haemorrhagic areas passed through the muscle nearly to the cavity of the uterus, the pathology then appearing to be an advanced chorionepithelioma, which had caused intra-peritoneal bleeding by perforation (Fig. 1). Sections were examined microscopically from the fundus and the paracervical tissue and were reported upon by my colleague, Dr. John Sturrock, as follows: "Uterine fundus is invaded by a typical chorionepithelioma which has ruptured through the peritoneal coat entirely (Figs. 2 and 3). The uterine cavity is not involved. Section of one ovary shows an active corpus luteum and maturing follicles. Section of the parametrial nodule shows typical chorionepitheliomatous infiltration with much blood extravasation (Fig. 4). Section through unruptured fundal nodule shows deep invasion by chorionepithelioma."

The patient made an uninterrupted recovery, but the A.Z.R. was found to be still positive 3 weeks after operation, so it was decided to give deep X-ray therapy to the pelvis as one knew that all the parametrial focus could not have been removed. At the same time her chest was X-rayed and thoroughly examined, but both these examinations were found to be absolutely negative. Vaginal examination 4 weeks after operation was found to be satisfactory. Six weeks later the patient reported again complaining of pain round her lower ribs on the right side posteriorly and stated she had had further haemoptysis. The A.Z.R. was again taken and found to be positive and now an X-ray of her chest was reported on as follows by Dr. R. McWhirter, who had taken especial interest in the case: "patchy areas of increased density now present in both infra-clavicular regions especially in the right and in the lower part of the lung fields again more on the right side, where there is some consolidation in the region of the costophrenic angle, which is obliterated. In view of history, probably metastatic changes."

On Dr. McWhirter's advice she was given X-ray therapy for her chest, but this was unavailing and her condition gradually deteriorated due to frequent haemoptysis and it was from this cause that she died 6 months after her operation.

It is very difficult, if not impossible, in

this case to suggest when the chorion-epithelioma began, and after which pregnancy or abortion, but it would appear, if the history she gave is correct, that the abortion in 1940 must have been its starting point. This would mean that it had been growing for nearly 2 years, which seems to be an unusually slow rate of growth, but as her periods were very irregular during this time, with periods of amenorrhoea and floodings, it is a possibility. The other hypothesis is that it was a very quick growing tumour following an abortion at the beginning of October, after 3 months amenorrhoea. There is no history of what she passed at the flooding following the amenorrhoea as a doctor had not been in attendance and there might have been a hydatidiform mole present. Haemoptysis, however, occurred 10 days after bleeding began, which would seem to indicate a much too early metastasis and certainly the pathological condition of the uterus would seem to indicate a growth of much longer standing. However, let the incidence be what it may, from the point of view of this paper, a chorionepithelioma would seem rarely to produce intra-peritoneal bleeding and very rarely indeed sufficient bleeding to fill the abdomen with blood and produce profound collapse.

Case 2.

The second patient is even of greater interest, and the condition apparently of greater rarity, as I cannot find any record of a similar case. This was also a case of severe intra-peritoneal bleeding due, so far as I could diagnose, to a perforation of a small artery at the base of the pouch of Douglas on the rectal wall by a very small ectopic tumour consisting of villi, which were undergoing hydatidiform degeneration, the tissue closely resembling a hydatidiform mole.

The history of this case was as follows: Mrs. H.; nullipara; age 24 years; married 3 years. The periods had been regular 7/28 until October 28th, 1942, when she had a period of amenorrhoea which lasted until December 10th, when she began to bleed per vaginam, the bleeding being preceded by 2 days pain, which became worse when the bleeding began. The pain was colicky in nature and came in spasms. She was violently sick on one occasion. The pain continued off and on for 2 further days and then disappeared, but the bleeding continued slightly until December 26th. She was sent to me as an out-patient on December 21st, when I found the uterus to be enlarged but not unduly soft; the cervix was not softened and was closed and except for a slight thickening of her left appendages, which were not unduly tender, nothing abnormal was found. I wrote to her doctor stating that I thought the patient was suffering from an early incomplete abortion, with very little left behind in utero and recommended ergotin pills in the first instance, suggesting that if the bleeding did not subside she should be admitted for a curettage. On December 26th the bleeding became more severe and on the morning of December 28th she was seized with severe abdominal pain most marked in the left iliac fossa and was sent to see me again as an emergency. On admission she felt very faint and broke out in a cold sweat and was violently sick. Her pulse was rapid and feeble, her temperature subnormal and she was in a state of collapse. On examination the abdomen was somewhat distended and tender and on vaginal examination there was a very tender mass to the left of and behind the uterus. I had no hesitation in diagnosing a tubal gestation and after arranging for a transfusion to be given, proceeded to perform a laparotomy. The peritoneal cavity was found to be full of blood and blood clot and, on examination of the

pelvic organs the uterus was found to be slightly enlarged but both Fallopian tubes seemed to be absolutely healthy and there were no signs of a tubal gestation on naked eye inspection and blood was not found to be exuding from the tubes nor was there any blood clot surrounding the ostia. Both ovaries were healthy. On further investigation a small mass, about the size of a 4 weeks ovum, was found surrounded by blood clot in the pouch of Douglas and this was found to be slightly adherent to the posterior peritoneal wall over the rectum, which had been somewhat denuded of peritoneum. This mass was removed with ease, but it was seen that bleeding was still going on, and on further inspection a small vessel in the denuded area over the rectum was seen to be spurting. This was ligatured with a mattress suture and all the bleeding ceased. The area was peritonized as much as possible and a pack inserted to be certain that all oozing would be controlled, as the patient's condition could not have withstood any further bleeding, however slight, and the abdomen was closed.

The pack was removed after 48 hours time, and further convalescence was uneventful, there having been no further bleeding or oozing and the patient left the ward in 3 weeks time. Examination of the tissue removed showed chorionic villi, and decidua lying in blood clot, there being no sign of any embryo. Many of the villi showed vesicular appearance, suggesting early hydatidiform change, and examination of further sections confirmed that hydatidiform degeneration was present in many of the villi. (Fig. 5.) The A.Z.R. was negative 3 weeks after operation and again 3 and 5 months later; when she was seen at this later date the patient was found to be well and her periods had been regular 6/28 being rather less profuse than before her operation.

This is also a difficult case to assess, but from the history and my examinations I think that she must have had a complete tubal abortion on or about December 10th, as on my first examination there was not any sign of tubal swelling or ectopic gestation present; whereas the tender mass felt a week later was due to the rapid growth of hydatidiform elements, which had been aborted completely from the tube when very small; these had undergone rapid growth and had penetrated through the peritoneum at the back of the pouch of Douglas, to cause the perforation of a small vessel on the rectal wall; this caused the profuse bleeding which gave rise to the acute symptoms of collapse and necessitated immediate operative treatment.

For their aid in the production of this paper I have to acknowledge my grateful thanks to Dr. John Sturrock for the microscopical work, to Dr. Rae Cripps for her drawing of the uterus with the chorion-epithelioma, and to Mr. J. Shearsby for the microphotographs.

Pregnancy Associated with Congenital Cystic Disease of the Lung

BY

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CYSTIC disease of the lung is a rare condition, though not as rare as was previously supposed. Combined with pregnancy it is rarer still, for a very large number of victims of this trouble die in infancy or early youth or are chronic invalids, and as a rule these older patients die with haemoptysis or sepsis due to acquired bronchiectasis. It is also known that where there is present one congenital abnormality it is not at all unlikely that others may be found and, combined with cystic disease of the lung, congenital heart disease, dextrocardia, congenital cystic disease of the kidney, and polycystic disease of the liver may be seen. The following case exhibits the truth of these statements:

Mrs. E. S., aged 24, was sent into an E.M.S. hospital because of pregnancy and supposed advanced tuberculosis of the apex of the right lung. When aged nine she had been in a sanatorium for a year, and an abscess in her neck was opened when she was thirteen but healed up well. She had some dyspnoea on exertion, but it is doubtful whether there was much real disability from this symptom. She was pregnant, a primigravida. It was on her attending an ante-natal clinic that the lung condition was noted. The condition of the lung was at once disclosed by an X-ray: "Cystic disease, right upper lobe, and probably middle or lower lobe. Heart and mediastinal contents pulled to right." This examination was made on entry.

After the Caesarean section Dr. Morton Gill made a special examination of the patient's lungs. His report is as follows:

Pale; gross clubbing of fingers and toes; trachea central; no displacement of heart.

Right chest: diminished expansion; increased tactile fremitus; impaired percussion note; harsh vesicular breath sounds; coarse bubbling rales accentuated by coughing; increased vocal resonance; no whispering pectoriloquy.

An X-ray of the abdomen and pelvis showed a normal pregnancy, but a breech one; and the pelvis, the measurements of which are given below, was distinctly of an anthropoid type.

Interspinous 23 cm., intercristal 26 cm., external conjugate 19.25 cm., Interischial 8 cm., arch contracted.

In view of the risk of haemorrhage from the lung, due to the strain of labour, breech presentation in a primipara with very little liquor amnii, and the slight malformation of the pelvis, it was judged better that the patient should not have the strain of labour.

On April 29th, 1943, she suddenly developed pains referred to the back, and it was clear that "labour" was commencing. She was taken to the theatre and spinal anaesthesia (heavy percaine) given and, as she was inclined to be nervous, a little gas and oxygen. The abdomen was opened by a median sub-umbilical incision, prolonged a little above the umbilicus on the left. The uterus was rectified and opened by a four inch incision in the midline, well down in the front. Very little liquor amnii escaped; the child was extracted by the breech with a little difficulty and breathed and cried at once. It was a female weighing 6½ lbs.

The cord was severed and the child handed to an assistant. On turning to the abdominal wound nothing could be seen save the foetal surface of the placenta. The uterine wall appeared to have disappeared. On raising and removing the placenta it was found that the uterus had split in the middle line right over the fundus and 3 to 4 inches down the back. The upper part of the

uterus was unusually thin, the thickness of the wall when contracted being only about $\frac{1}{4}$ inch.

Pituitrin was given and the two halves of the uterus pressed together. The wound in front, over the summit and down the back, was closed by two layers of interrupted No. 2 catgut sutures; the first taking in the whole thickness down to the decidua, the second, taking up peritoneum and a little muscle, put in Lembert fashion, covering the first line of sutures. On the whole the uterus contracted well, and the bleeding, though a little more than normal, was not excessive, and the patient left the table in good condition.

Her convalescence was normal. Quite apart from the action on the lungs of the strain of labour it is a question whether the upper part of the uterus would not have undergone spontaneous rupture.

The baby was breast-fed. By X-rays there was no abnormality seen in its lungs and when it left hospital it was well over birth weight.

Literature on the effect of congenital cystic disease of the lung in association with pregnancy is surprisingly scanty. With the aid of the Librarian of the Royal Society of Medicine; Dr. Nicholson J. Eastman, Head of the Department of Obstetrics in Johns Hopkins Hospital; and Dr. J. P. Greenhill, Editor of the American Year Book of Obstetrics, to whom my thanks are due, I have been able to trace records of only two other cases. Reisner[1] notes incidentally in a paper on congenital cystic disease of the lung that, in a case where congenital cystic disease was associated with pregnancy, cough and asthma became worse after the birth of the second child.

A second case, reported by Garnier,[2] is that of a woman of thirty-eight, a primigravida, in whom the affection was at first thought to be tuberculous. She carried to full term but was ailing from the thirtieth week onwards. After two days of "labour" pains without the os dilating, a Caesarean section was done. She died 30 hours after operation with dyspnoea, which had begun some 12 hours after operation. The whole of the upper right lobe was cystic and the cavities filled with mucopurulent fluid. The anaesthetic used for the operation is not noted. There is no doubt however that spinal anaesthesia, or local anaesthesia, is the anaesthetic of choice in these cases and it is doubtful whether the strain of labour is ever justifiable in the patient's interest.

My thanks are due to my colleagues Drs. Morton Gill and Berridge for clinical and radiological reports, to Dr. Hawes for the anaesthetic, and to Professor F. J. Browne for advice.

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A Case of Retroperitoneal Pelvic Ganglioneuroma

BY

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THE following case of a ganglioneuroma arising from the presacral sympathetic plexus is reported, not only because such tumours are rare, but because reference to the literature showed that pelvic ganglioneuromata have fairly constant clinical and pathological characteristics, and a brief note may assist others to make a correct diagnosis.

Clinical History. The patient was a young woman student aged 21, single. She was referred to me by a physician who found an abdominal tumour during the course of a routine health examination. The patient had been aware of the swelling for at least 6 months, but had been doubtful if it was really abnormal and so had not troubled to report it. She was in excellent general health, and nulliparous. Menstruation was regular and normal with a 5/28 days cycle, and almost painless, the last period being 1 week before examination. Digestion and bowel action were normal, and apart from the swelling her only symptom was inability to hold her water so long as formerly.

On examination of the abdomen a smooth rounded swelling was found rising out of the pelvis, and extending half-way to the umbilicus, with a slightly greater prominence on the right side. The tumour was of moderately firm consistence, without fluid thrill, but it was doubtful if it was a soft solid or a tense cyst. On rectal examination the tumour was found to be separate from the uterus, which was itself normal, and displaced to the left by the tumour. The left ovary was felt to be normal, but the right could not be felt. The tumour was fixed to the pelvic wall on the right and posteriorly, the rectum being displaced to the left. The tumour appeared to be a soft solid, but this observation was uncertain, and in view of the patient's age a broad ligament cyst was thought to be the most likely diagnosis.

Operation. On November 23rd, 1942, under general anaesthesia, the abdomen was opened by a right paramedian incision, and the tumour was found to be retroperitoneal, and situated obliquely, the lower pole lying to the right side of the pelvis, and the upper pole near the midline over the sacral promontory. The uterus and adnexae, which were normal, were displaced forwards and to the left, the peritoneum of the recto-vaginal pouch and right broad ligament being stretched over the tumour. After incising the peritoneum over the tumour it shelled out fairly easily, and was stripped from the vessels of the right pelvic wall. Posteriorly there was a little difficulty, where the mass was fixed by fibrous bands to the tissues over the sacrum. Having demonstrated the integrity of the ureter, and after tying a few small vessels, the posterior peritoneal incision was sutured, and the abdomen closed.

The immediate condition of the patient was good, and she made a rapid and uneventful recovery. There were no urinary difficulties, or abnormal action of the bowel.

FIG. 1.

Pelvic ganglioneuroma. The photograph shows the point of attachment to the presacral tissues, and fibrous bands and nerve filaments pierce the capsule at this point. The flat lower edge of the specimen is the result of fixation in one position.

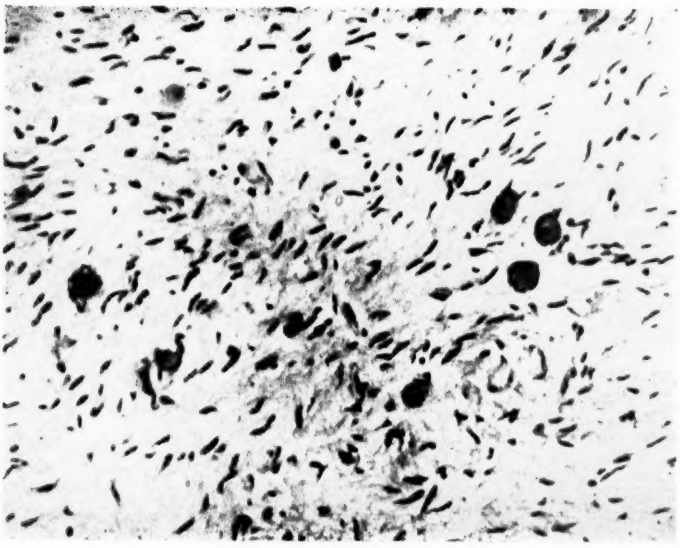

FIG. 2.

Pelvic ganglioneuroma. Microscopical section showing ganglion cells.

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Specimen. The tumour when measured was 6 × 4 × 3½ inches. It was smoothly rounded, and had an intact capsule except at the original point of fixity to the presacral tissues, where a few filaments were attached. It was solid, but soft, and on bisection the cut surface was a uniform yellowish-white colour (Fig. 1). Microscopic examination showed that the tumour was a typical ganglioneuroma, consisting chiefly of bundles of non-myelinated nerve fibres, but with many groups of ganglion cells, many of these showing vacuolation. (See Fig. 2.) From its position the tumour was thought to have arisen from the right hypogastric plexus.

After-history. After 6 months the patient was re-examined. She stated that there had been no alteration in micturition, bowel habit or menstruation, but she noticed that her right foot remained permanently warm irrespective of changes in the environmental temperature. She regarded this curiosity as an advantage, and was in excellent general health.

Commentary.

Ganglion cell tumour was first described by Loretz[1] in 1870, and pelvic ganglioneuromata were reported by Chiari[2] in 1898, and by Cripps and Williamson[3] in 1899.

Tumours of the sympathetic nervous system and suprarenal medulla are of two types; the undifferentiated forms which occur most frequently in children (sympathicoblastoma or neuroblastoma), and the mature forms (ganglioneuroma) which are usually found in young adults, and which are alone considered in this article. Ganglioneuromata may occur in any part of the sympathetic system, and over 160 cases have now been recorded in various sites throughout the body, and among these were 15 cases of pelvic origin. (Raska and Skorpil[4]). Pelvic ganglioneuromata may arise from the sacral or coccygeal sympathetic cord, from the hypogastric plexus, or from the utero-vaginal plexus, the uterus itself (Fingerland and Sikl[5]), or the ovary (Schmeisser and Anderson[6]). In the present summary only ganglioneuromata of retroperitoneal pelvic origin will be considered, and these are conveniently described as presacral, precoccygeal or intraligamentary. This subdivision is not always accurate, as most of these tumours are large and displace the pelvic peritoneum as they rise upward into the abdomen; and in other cases tumours of lumbar origin may extend downward into the pelvis, so that the precise site of origin of any particular tumour may be doubtful, except in so far as its point of attachment to the pelvic sympathetic plexuses may be demonstrated. The table shows the recorded cases of these tumours with a few details about them.

It will be seen that all these cases except one were female, and this may be partly due to the fact that pelvic examinations are more frequently made in young women than men. This sexual preponderance is not so evident when these tumours arise in other sites; e.g. in Kehrer's[7] series of paralumbar ganglioneuromata there were 12 female cases and 10 male cases.

The average age of these patients was 24 years, and 11 out of 16 cases were aged between 20 and 30 years. (The age was not stated in one case).

Ganglioneuroma is a tumour of slow growth, and in most cases the tumour was large before its discovery. In the case of von Salacz[8] for example, the tumour was known to have been present for 14 years and weighed 2730 grams when removed. The clinical features are not fully described in all the case reports, but in general the symptoms were remarkably slight, no doubt because of the slow growth of the tumours. Several of the cases were only

discovered during labour or pregnancy, and would not otherwise have been found. Backache, or slight abdominal discomfort were noted, and sciatic pain in 2 cases, but severe pain was not mentioned. Apart from constipation, pressure symptoms are unusual with pelvic ganglioneuromata, although Kehrer[7] listed many such symptoms with ganglioneuromata in other sites in the abdomen. There was no record of interference with pelvic sympathetic pathways, and menstruation was normal in all the cases except one. Six cases were pregnant when the tumour was discovered, which suggests that endocrine function is undisturbed.

The physical signs found in the present case are very typical. In most of the cases there was a soft or moderately firm tumour of oval shape and large size, situated to one side of the midline, fixed posteriorly, and which displaced the uterus and rectum to the opposite side. Though a tumour of the broad ligament was often correctly diagnosed, its origin from nerve tissue was never considered. Whichever part of the pelvic sympathetic system gave rise to the tumour, the final anatomical arrangement was very similar, as the pelvic peritoneum, including that of the broad ligament and mesosigmoid, was displaced and stretched over the tumour. Although all the tumours listed here were histologically benign, and the long histories confirmed this, many of the reports mentioned dense adhesions between the tumour and the pelvic vessels and sacrum. I was very fortunate that such adhesions were not found in the present case. In Kehrer's case[7] the right iliac artery was torn and sutured during removal of the tumour, and a ureteric fistula followed the operation. In the case of von Salacz[8] the common iliac artery required ligature, and haemorrhage from this and other vessels was such that the patient died. In 3 cases (Cripps and Williamson,[3] Evans and Francona,[9] Kehrer[7]) a transient peroneal palsy followed the operation. Sippel[10] and Stoeckel[11] were compelled to remove the tumours piecemeal, and both Fels[12] and Turner[13] stressed the difficulty of the operation. Even in the case of Evans and Francona,[9] when the tumour was easily removed, the operation was complicated by acute gastric dilatation and collapse of the patient.

Six of these patients were pregnant, and these cases show the danger of neglecting to make a pelvic examination during pregnancy, for in 3 cases obstructed labour due to a previously undiagnosed tumour led to maternal death. (Beneke,[14] Strassmann,[15] Strada[16]). In the case of von Salacz[8] Caesarean section was necessary in a first pregnancy, but death followed excision of the tumour early in a second pregnancy. In Sippel's case[10] Caesarean section was performed, and the tumour was successfully removed at the same time; and in Turner's case[13] normal delivery followed a successful operation early in pregnancy.

Diagnosis.

These tumours were often correctly diagnosed as tumours of the broad ligament before operation, though their true nature was not suspected until microscopical sections were made. The points which might suggest the diagnosis of a pelvic ganglioneuroma are the age of the patient, the slow growth and slight symptoms, and the discovery of a solid tumour of rounded form, fixed to the presacral tissues, and displacing the uterus. At operation the adhesions to the pelvic wall may be a striking feature. Diagnosis from retroperitoneal lipoma or sarcoma may be impossible, but a broad ligament fibroid would be distinguished as being harder and attached to the uterus rather than to the sacrum, and a broad ligament cyst is usually obviously fluctuant as such cysts are seldom tense.

Author	Age and sex of patient		Site of tumour	Recorded history	Size of tumour	Treatment or other notes	Result
Chiari.[2] (1898)	22	F.	L. Presacral	——	"Double fist"	Operation. (Original reference unobtainable.	A.
Cripps and Williamson.[3] (1899)	21	F.	L. Presacral	Seven years abdominal discomfort and backache. Irregular periods.	12 x 8 cm.	Operation. Tumour very adherent. Post-operative peroneal palsy.	A.
Berblinger.[17] (1918)	50	F.	Presacral	Many years history of sciatic pain.	"Walnut"	Found at postmortem.	D.
Stoeckel.[11] (1923).	19	F.	L. Presacral	No symptoms. Found during investigation of gonorrhoeal discharge.	"Fist"	Operation. Very adherent. Removed piecemeal.	A.
Sipple.[10] (1923)	24	F.	R. Presacral	No symptoms. Found during pregnancy.	" Fist"	Caesarean section. Tumour very adherent. Removed piecemeal.	A.
Strada.[16] (1927)	23	F.	Presacral	Obstructed labour. No previous symptoms.	Not stated	Caesarean section. Peritonitis.	D.
Fels.[12] (1933)	32	F.	L. Presacral	Tumour present 21 years. Sciatic pain.	" Fist"	Operation. Very adherent.	A.
Kehrer.[7] (1934)	25	F.	R. Presacral	Slight lower abdominal pain.	12 x 7 cm.	Operation. Densely adherent. Right iliac artery ligatured. Ureteric fistula. Peroneal palsy.	A.
von Salacz.[8] (1936)	22	F.	R. Presacral	Tumour present 8 years. Caesarean section 2 years previously. Now 2 months pregnant. No symptoms.	23 x 12 x 8 cm. 2,730 grm.	Operation. Dense adhesions. Right common iliac artery ligatured.	D.
Evans and Francona.[9] (1940)	27	F.	R. Presacral	Backache and constipation.	14 x 12 x 7.5 cm. 600 grm.	Operation. Post-operative collapse. Peroneal palsy.	A.
Turner.[13] (1940)	27	F.	R. Presacral	No symptoms. Found when 2 months pregnant.	12x12x8 cm. 700 grm.	Operation. Dense adhesions. Normal delivery later.	A.
Clayton. (1943)	21	F.	R. Presacral	No symptoms.	15 x 10 x 7.5 cm.	Operation.	A.
Strassmann.[15] (1913)	30	F.	Precoccygeal	Obstructed labour. No previous symptoms recorded.	"Double fist"	Failed forceps. Caesarean section. Nature of tumour discovered at postmortem.	D.
Alezais and Imbert.[18] (1907)	6	M.	Precoccygeal	——	——	(Original reference unobtainable.)	
Beneke.[14] (1901) (Case 1)	25	F.	Intraligamentary	Obstructed labour. No previous symptoms recorded.	"Child's head"	Craniotomy. Peritonitis. Nature of tumour discovered at postmortem.	D.
Neumann.[19] (1928)	14	F.	Intraligamentary	Not recorded.	40 grm.	Operation. No details recorded.	D.
Zagarese.[20] (1933)	—	F.	L. Intraligamentary	Tumour present 5 years.	54 x 42 cm. 6.25 Kgrm.	Operation.	A.

Certain other cases which have appeared in previous reports have been excluded as reference to the original articles showed that these cases were not typical benign ganglioneuromata, e.g., Jones, McN.[21] Giepel,[22] Law.[23]

SUMMARY.

A case of pelvic extraperitoneal ganglioneuroma arising from the hypogastric sympathetic plexus is described, and the literature summarized.

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Chronic encephalitic mother and her two healthy children. Elder, female, born 1924, during the acute attack of epidemic encephalitis. Younger, male, born 1940, after 16 years of chronic Parkinsonism. (Photo. October 1941.)

UNIV. OF MICH.

A. J. H.

Epidemic Encephalitis and Pregnancy

BY

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IT is now well known that when acute epidemic encephalitis occurs during pregnancy, labour may be normal and the child in every way healthy; also that a woman suffering from chronic encephalitis can bear healthy offspring. The following case illustrates the truth of both of these statements, in a somewhat unusual way, in the same woman.

S.J.X[1] was married in August 1923, when 22 years of age. In April 1924, when 8 months pregnant, she had a severe attack of epidemic encephalitis, with delirium, diplopia and lethargy. A healthy female child was born at term on May 25th. Labour was normal. Soon after this, symptoms of Parkinsonism set in, and for the next 18 months the woman was bedridden. Salivation was very troublesome. Early in 1926 tincture of belladonna was prescribed in moderate doses. The improvement was rapid and marked, so that in a short time she was able to get up, and, gradually, to do her housework again. The salivation was completely controlled. From October 1926, when she first attended the Clinic at the Sheffield Royal Hospital, until 1940, her condition remained practically unchanged. She was a Parkinsonian in Stage 1. During these 14 years she attended regularly, and was taking one dram of tincture of belladonna daily. The rate of movement in her arms, as tested by the apparatus described in *The Lancet*, 1927, ii, 1009, had not deteriorated during 11 years. In 1927 it was 51 per cent in the right arm and 44 per cent in the left arm. In 1938 it was still 51 per cent in the right arm and 42 per cent in the left arm. By this date the daughter (see Plate), born within a month of the mother's acute attack, had grown into an exceptionally big fine young woman. In August 1940, the mother became pregnant again, and gave birth to a healthy male child at term on December 1st, 1940. Labour was easy; the child weighed 6½ pounds. There was complete absence of lactation, owing to the fact that she had continued taking the same dose of belladonna throughout her pregnancy. The photograph, taken in October 1941, shows the Parkinsonian mother and her two children. The boy weighed 28 pounds at 10 months old. The mother has become rather more bent over, and is not able to do much housework, or nurse the child. The second pregnancy has activated the progress of the Parkinsonism, which has now reached Stage 2, that is she is partially dependent. Her condition to-day, September 1943, remains practically the same.

This case shows that a woman who has been Parkinsonian for 16 years may not only become pregnant, but that the gestation may be in every way normal, labour easy, the child healthy, and that it may not seriously advance the disease. Also, that not only can a daily dose of one dram of tincture of belladonna continue to give relief for 11 years without increase being needed, but that the taking of it through-

out gestation has no deleterious effect on the offspring. The only effect was the complete inhibition of lactation. This is only what one would expect, seeing the long-known use of the belladonna plaster to stop lactation. In this connexion, it is well to bear in mind that in persons taking one of the atropin group, the sweat is inhibited also, and that hyperpyrexia even of fatal issue may occur in such persons if exposed to hot sunshine. Astley Cooper[2] called attention to this danger, of which I have seen three or four cases among Parkinsonians. A similar hyperpyrexia may even occur when the dosage is only such as comes from belladonna plasters on the breasts. In 1911 I saw a woman with a temperature of 105°F., which had followed sitting in the sun for some hours, while the plasters were on the breasts to check lactation. Although the pyrexia continued for some days during which she was very ill, she made a complete recovery.

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CRITICAL REVIEW

Endocrine Therapy in Gynaecology and Obstetrics

BY

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DURING the past 20 years, since Allen and Doisy[1] observed the oestrous cycle of the mouse by means of vaginal smears, endocrine therapy in gynaecology and obstetrics has passed through a period of infancy and adolescence. As is so often the case with a child the early birthdays seem to be the more memorable, and the milestones of this growing period seem chiefly to have appeared during the pre-war days (Aschheim and Zondek's[2] discovery of a gonadotrophin from human pregnancy urine, 1927; the isolation of the pure crystalline ovarian hormone, 1929; the isolation of a pure crystalline male hormone, 1931; the isolation of progesterone, 1934; the isolation of the synthetic oestrogen stilboestrol, 1938). Though the advance has been less spectacular during the 5 years of war, much ground has been consolidated, and a perhaps more sober outlook on the role of clinical endocrinology has developed. For this reason most of the work reviewed here has been done in these last 5 years, and though it has been necessary to include reports of claims which have not yet been thoroughly substantiated, an earnest attempt has been made to present a well-balanced picture not overcoloured with the high lights of enthusiasm nor yet darkened with the gloomy shades of conservative pessimism.

SYNTHETIC OESTROGENS: THE DEVELOPMENT OF CHEAP ORAL THERAPY.

The synthetic oestrogen 4:4′-dihydroxy-2β-diethylstilbene (stilboestrol) was isolated by Dodds, Goldberg, Lawson and Robinson[3] in 1938, and was reported to possess biological activity similar to oestrone (Dodds, Lawson and Noble[4]). Reports on its clinical effects were made to the Therapeutic Trials Committee of the Medical Research Council (Winterton and McGregor[5]; Kellar and Sutherland[6] Bishop, Boycott and Zuckerman[7]). Compared with oestrone it was found to be highly active, especially when given by mouth. Mild toxic effects were noted. Other authors (e.g. Varangot[8]; Shorr, Robinson and Papanicolaou[9]) however reported vomiting, abdominal distress, diarrhoea or even cutaneous rashes in up to 80 per cent of cases, and the Council on Pharmacy and Chemistry of the American Medical Association witheld their recognition of the compound as being suitable for general use. In the past 5 years, however, many thousands of patients have been treated with stilboestrol, and it is possible to place the toxicity factor in its true perspective. Of 3,680 cases which the author has been able to collect from 88 clinical reports, in which the toxic effects are specifically recorded, they occurred in 17 per cent and are described as serious in only 3.5 per cent. They are more likely to take place when high doses (1 to 5 mg.) are given than with small doses (under 1 mg.). The majority of patients complaining of toxic effects in this series were receiving more than 1 mg. daily. Toxic symptoms have never been recorded in pregnant or puerperal women, even when 1 gram

(1,000 mg.) was given over a period of 3 to 10 days (Abarbanel and Klein[10]). These women are, of course, already saturated with self-secreted oestrogen. On the other hand menopausal women and others suffering from oestrogen deficiency are not only relatively responsive to small doses but also complain more frequently of toxic symptoms, especially when high doses are given.

Shortly after the discovery of stilboestrol Campbell, Dodds and Lawson[11] reported the isolation of another synthetic oestrogen, hexoestrol (dihydro-stilboestrol) and this was submitted to clinical trial (Bishop, Bowes, Boycott, Kellar, MacGregor and Murless[12]). Though highly active it was not found to have the same degree of oral potency as stilboestrol. Freed, Eisin and Greenhill,[13] for instance, found it to be one-fifth as effective, whereas Bieren and Compton[14] believe it to be 10 times as weak. It is, however, less liable to produce toxic effects.

Another oestrogen, dienoestrol, synthesized by Dodds, Goldberg, Lawson and Robinson,[15] has been thought to be suitable for clinical use. So far the only publication on its clinical effects comes from Barnes.[16] She found it to be 10 times more active than stilboestrol, but as it was given to puerperal patients there was no opportunity to test its toxicity. My own experience of the compound is so far limited; I have not yet, however, encountered any toxic effects in non-pregnant women in daily doses of up to 4 mg. My impression is that it is 2 or 3 times as active as stilboestrol.

In 1942 a synthetic oestrogenic compound unrelated to stilboestrol was announced by Blanchard.[17] It has been given the name "octofollin" and has been reported on clinically (Freed, Eisin and Greenhill;[13] Hufford;[18] and Roberts, Loeffel and MacBryde[19]). It would appear to have about the same potency as hexoestrol and is more expensive weight for weight than stilboestrol, but so far toxic effects have been recorded only in a small number of cases of one series.[13]

The clinical role of synthetic oestrogens is to provide compounds of high oral activity which are very much cheaper than the natural oestrogens, and which are non-toxic. Despite its greater toxicity, however, stilboestrol is at present the most commonly used oestrogen.

Modes of Administration.

The tendency to adopt oral therapy in preference to intramuscular injection has already been noted in the case of oestrogens. Orally active androgenic and progestogenic compounds are now also in common use. In 1938 Inhoffen and Hohlweg[20] synthesized ethisterone (ethinyl testosterone, anhydro-oxyprogesterone or pregnenineolone) and showed that it possessed progesterone-like biological activity when given by mouth, though progesterone by injection was 4 times as active. It is capable of producing toxic symptoms in high doses, and it has not been shown to induce complete progestational changes in the endometrium biologically. It has, however, proved a moderately effective substitute for progesterone. In 1938 Miescher and Tschopp[21] reported on the oral activity of methyl testosterone and it became available for oral use as an androgen (Foss 1939[22]). It is said to be a third as effective by this route as testosterone propionate is by injection. Administration of steroid hormones in the form of "linguets" (small tablets placed under the tongue or between the upper lip and the gum) was introduced in 1940,[23, 24] and it was claimed that a higher degree of absorption resulted from the buccal mucous membrane directly into the blood stream than by alimentary assimilation.

The advantages of oral therapy over intramuscular injection are not only that a slightly painful prick is avoided but also that a more constant level of hormone in the blood stream is achieved especially if the orally active compound is administered in frequent divided daily doses. Nevertheless there is great wastage of hormone and the amount of active substance absorbed is to a great extent unpredictable. The most economical method of steroid hormone administration and one which ensures a constant blood hormone level over a very long period of time is by subcutaneous implantation of a compressed or fused pellet of the crystalline hormone. This method was introduced by Deanesly and Parkes in 1937,[25] and first applied to the human subject in 1938 (Bishop[26]). It has since been used extensively in the case of oestrogens and androgens. Unfortunately the implantation of progesterone is not well tolerated and the pellet is extruded through the skin after a few weeks. Testosterone propionate suffers the same fate, but testosterone, oestrone, oestradiol dipropionate, stilboestrol and ethisterone are well tolerated. The rate of absorption from the surface of the pellet varies with the individual hormone. Compared with the rate of absorption of orally active compounds of steroid hormones or of their esters given by injection, it is very prolonged. A 100 mg. compressed pellet of oestradiol, for instance, remains effective for more than 2 years (Bishop and Folley[27]). Such large doses, however, are not generally appropriate to gynaecological disorders where endocrine therapy is usually limited to short periods, though 50 mg. oestrogen implantation may be efficacious in cases of the menopausal syndrome.

The Scope of Oestrogen Therapy.

The induction of uterine haemorrhage in a human castrate by injection of oestrogen (Kaufmann[28]) made a great impression on gynaecologists, and it was hoped that at last a cure for amenorrhoea had been discovered. It soon became clear, however, that, as Novak[29] remarked as early as 1934, to use oestrogen in amenorrhea "is to push the pendulum of the rundown menstrual clock for a single idle, incomplete beat, when what we need is something to wind the clock." Nevertheless to-day oestrogen still features quite prominently in the treatment of amenorrhoea. This is partly because of the desire of both the patient and the doctor to demonstrate that the uterus can be made to bleed. Nevertheless in a certain small percentage of cases it does seem that oestrogenic stimulation of an underdeveloped uterus may render it responsive to the patient's own ovarian secretions and result in establishment of a normal menstrual rhythm. In the past ten years, however, there has developed a sober recognition of the fact that oestrogens are incapable of stimulating either the ovary or the pituitary and that amenorrhoea is almost always an incidental manifestation of organic disease, nutritional deficiency, environmental change, emotional shock or of some endocrine syndrome such as pituitary deficiency, overactivity of the adrenal cortex or thyroid disturbance. Hisaw,[30] Corner[31] and Zuckerman[32] have reported cyclical bleeding following prolonged daily injections of oestrogens in castrate monkeys and continuous oestrogen therapy, by means of subcutaneous pellet implantation for instance, may prove a suitable means of providing the endometrial stimulus required.

The most incontrovertible indication for oestrogen therapy is relief of menopausal symptoms and reversal of post-climacteric atrophic vaginal changes. Dosage depends on whether ovarian regression is recent or remote. Though reversal of senile vaginal changes sometimes requires concentrated

courses of 1–5 mg. doses which often induce uterine haemorrhage and tenderness of the breasts, a high proportion of the cases of the menopausal syndrome respond satisfactorily to daily oral doses of less than 1 mg. In an effort to ensure success overdosage is becoming increasingly fashionable. It tends to produce unpleasant symptoms similar to those seen in pre-menstrual tension. Furthermore, it has been shown (Bishop and McKeown[33]) that high doses of oestrogen render the organism insensitive to previously minimal effective doses. The weaning period is therefore prolonged. If stilboestrol is used initial daily doses should be 0.1 –0.5 mg.

Oestrogen has been employed with success to prevent painful engorgement of the breasts (Foss and Phillips,[34] Kurzrok and O'Connel,[35] Stewart and Pratt[36]) in non-nursing mothers. The effect is not due to inhibition of lactation (Meites and Turner[37]). Abarbanel and Klein[10] have shown that huge doses of stilboestrol (1,000 mg., in 3 days) will not inhibit lactation in the nursing mother in whom the lactation stimulus is maintained by suckling. The initial dose should be 10, 25 or even 50 mg. if stilboestrol is used, depending on whether the oestrogen is being given to prevent or to relieve breast engorgement. The daily dose should be rapidly reduced to 5 or even 1 mg. over a period of a week to 10 days (Abarbanel, Aranow and Goodfriend[38]). Provided the initial dose is adequate prevention or relief is invariably assured.

Oestrogen even in high doses not only fails to inhibit established lactation in the nursing mother, but also fails to diminish the quantity of an excessive milk yield or to stop persistent lactation (Stewart and Pratt;[36] Abarbanel, Aranow and Goodfriend[38]).

Oestrogen has been employed in an attempt to increase the motility of the pregnant uterus. It appears to be completely ineffective as an early abortifacient (Abarbanel;[39] Jeffcoate[40]). It has, however, been successfully employed as an adjuvant to posterior pituitary extracts and quinine in the medical induction of labour. It is given hourly for about 12 hours in 10-20 mg. doses. It has been used successfully in high doses (up to 50 mg.) given every 2 hours for about 5 doses in cases of uterine inertia (Abarbanel[39]). It has also been recommended in cases of missed abortion with success in about 50 per cent of cases (Jeffcoate[40]). High doses must be given as in the induction of labour.

Progestogen Therapy in Uterine Bleeding and in Threatened and Recurrent Abortion.

The two chief indications for progestogen therapy are functional uterine bleeding and recurrent and threatened abortions.

(1) With regard to *functional uterine haemorrhage* opinions as to the efficacy of progestogen therapy vary considerably. For instance, Wilson and Elden[41] claimed to have controlled the bleeding in 5 cases with total doses of under 1 mg. of progesterone. Mishell[42] obtained satisfactory results in 2 out of 4 cases. MacGregor[43] controlled haemorrhage in 7 cases with no immediate recurrence of abnormal bleeding. Wiesbader[44] treated 20 patients with ethisterone; 2 showed progestational endometrial changes. 200-240 mg. given during the 2nd half of the cycle maintained normal and cyclical bleeding. Gaines, Geist and Salmon,[45] on the other hand, found only 3 out of 14 cases slightly improved with daily doses of 30 mg. and total dosage of 570-3,480 mg. Seegar Jones and te Linde[46] have used progesterone only in cases of proved endometrial hyperplasia which have failed to respond to thorough curettage. They give 5 mg. daily (or 30 mg. of ethisterone)

for 10 days during a bleeding episode. Administration is repeated for 7 days commencing 9 days before the expected onset of the next bleeding phase, and for 4 days commencing 6 days before the third period. They claim 26 symptomatic cures out of 28 cases and the majority showed no recurrence of excessive bleeding following this therapeutic regime, even though followed up some years later. On the other hand, some authors are sceptical of the role of progestogen in the treatment of functional menorrhagia. For instance, Hamblen[47] in a series of 28 patients has failed to arrest episodes of oestrogenic bleeding with up to 15 mg. of progesterone, nor could he find any progestational change in the endometrium. Frequently the bleeding was actually increased in amount. Indeed Zondek and Rozin[48] have shown that progestogen can induce bleeding both in normally menstruating and amenorrhoeic women, and Zondek[49] has advocated the use of progesterone in the treatment of amenorrhoea.

(2) *Recurrent and threatened abortion.* The value of progestogens in this condition has always been the subject of controversy. There are those who draw attention to the fact that a history of previous abortions does not justify the supposition that the pregnancy under treatment would have terminated in abortion had treatment been withheld. For instance, Malpas[50] has calculated that the chances of a successful pregnancy following 4 successive abortions is 6 per cent, following 3 27 per cent and 2 62 per cent. MacGregor and Stewart[51] point out, however, that in a number of the reports on progestogen therapy (Kane;[52] Elden;[53] Bishop[54]) the percentage of successful pregnancies recorded is higher than that expected from Malpas's calculations. Others who have observed a high incidence of live births following progestogen are Mason;[55] Kotz, Parker and Kaufman;[56] and Soule[57] (threatened abortion). Despite the view expressed by Hamblen[58] that progesterone does not effect the pregnanediol excretion and may actually precipitate abortion by depressing the metabolism of intrinsic progesterone, it would seem that in a certain group of cases this type of therapy is in fact effective. Though Kane's results were obtained with very small doses (single doses of 1/25 Rab. U.) it is probably necessary to give doses of the order of 5 mg. Browne, Henry and Venning[59] have shown that the corpus luteum of pregnancy produces 5–10 mg. daily up to the 70th day and that in the 4th or 5th month the placenta produces 20–50 mg. daily. It is clear that progestogen deficiency is not the only cause of recurrent or threatened abortion. Kotz, Parker and Kaufman[56] refer also to nutritional deficiencies and defective germ plasm. They believe that recurrent abortions represent a milder stage of one of the conditions governing sterility and may in some cases be due to sperm deficiencies. They therefore postulate that each time such a woman conceives she has a better chance than last time of carrying the pregnancy to a successful termination. Irving[60] states that the incidence of foetal abnormalities in spontaneous abortion is 70 per cent. There seems to be good reason to commence treatment as early as possible and not to wait until symptoms appear or until the stage of pregnancy at which the previous abortions occurred. It is a characteristic feature of women who habitually abort that they conceive easily and I have adopted the practice of giving progestogen during the last week of each cycle until a period is missed and then applying the hormone constantly during the early stages of the pregnancy. Progesterone implantation would be an ideal method of treatment, but unfortunately the pellets are almost invariably extruded. Ethisterone pellets

are so slowly absorbed that it is doubtful whether an adequate level of dosage can be obtained by this method.

Androgen Therapy and Functional Uterine Bleeding.

The use of androgens in gynaecology is now well-established though there is still some natural hesitancy about employing substances which are known to be capable of producing such masculinizing effects as growth of hair on the face, acne, deepening of the voice and enlargement of the clitoris. Papanicolaou, Ripley and Shorr[61] have demonstrated inhibition of the menstrual cycle and regression of the vaginal smear to the menopausal type with daily doses of 25 to 50 mg. of testosterone propionate. Foss[62] produced atrophy of the endometrium with total doses of 300–2,000 mg., and Gaines, Geist and Salmon[45] found that 300–1,000 mg. suppressed the endometrial cycle and led to amenorrhoea. Nevertheless it has been shown that smaller doses are completely effective in controlling bouts of excessive bleeding and restoring normal cycles. For instance, Sturgis, Abarbanel and Nader[63] were able to stem the excessive flow with 10 to 30 mg. and stop it with 120 mg. and Mazer and Mazer[64] found that 30–120 mg. a month was sufficient to control functional uterine bleeding without disturbing the menstrual cycle or inducing regressive endometrial changes. Leff[65] found that 2 or 3 courses of 300 mg. a month would restore normal cycles for 6–8 months without producing endometrial or vaginal smear changes or signs of masculinization. Geist and Salmon[66] observed that up to 300 mg. a month produces an immediate control of functional uterine bleeding in 91 per cent of cases and in 87 per cent the effect was lasting. Such doses did not inhibit menstruation or change the endometrial pattern, whereas doses of 500 mg. or more, given early in the cycle, inhibited the pituitary and produced amenorrhoea, and in some cases masculinization. The beneficial effect of the lower doses was more evident in older patients, whereas in the younger group there was a tendency to recurrence of the excessive bleeding, which could however be prevented by giving a maintenance dose of 10–20 mg. weekly for some months following the re-establishment of normal cycles. Greenblatt[67] has reported on the administration of androgens by implantation and finds that 400 mg. of testosterone will control the bleeding without changing the endometrial pattern. Salmon, Geist, Gaines and Walter[68] find implantation unsatisfactory but 3 years experience of injection treatment has shown immediate improvement in 97.7 per cent of their cases and apparent cures in 66.6 per cent. Berlind,[69] using methyl testosterone orally, found that as much as 3,000 mg. a month (corresponding to 1,000 mg. of testosterone propionate by injection) did not produce masculinization and suggests that this compound is therefore less likely to induce masculinization than testosterone propionate. This is in agreement with Geist and Salmon's observation that doses of testosterone propionate over 500 mg. a month are apt to produce masculinization. It would seem that androgen therapy is most certainly the treatment of choice at present in cases of functional uterine haemorrhage. The chief objection to its use at this moment is that it is still very costly.

Androgens have been employed to prevent postpartum breast engorgement (Beilly and Solomon[70]) and also to alleviate menopausal symptoms (Kurzrok, Birnberg and Livingston[71]). Geist and Salmon,[66] however, have not found androgens as effective as oestrogens in the menopausal syndrome and use them only in cases which fail to respond to oestrogens or where there

is menopausal menorrhagia or irregular bleeding, or where oestrogens produce uterine haemorrhage. They give them in doses of 10–25 mg. weekly. Since oral oestrogens are usually completely satisfactory one would wish in using androgens as an alternative to give them by mouth also, and methyl testosterone is very much more costly than the synthetic oestrogens.

Dysmenorrhea and the Sex Hormones.

This is not the place to enter into a detailed account of the theories of functional dysmenorrhoea. They are complicated by the difficulties of correlating the features of uterine motility in the lower animals with those of the human subject, and of obtaining truly physiological records of the contractions of the human uterus. At the moment the most acceptable theory of uterine mobility appears to indicate that during the oestrogenic phase of the cycle uterine contractions are of relatively high frequency and low amplitude, whereas during the luteal phase contractions occur less often but are of higher amplitude. It may nevertheless be the case that amplitude is not the factor which governs painless or painful contractions. There is evidence to show that the pain may be due to a disturbance of the autonomic innervation of the uterus or that it may be caused by ischaemia of the muscle. It has been suggested that dysmenorrhoea is a sympathetic phenomenon leading to vaso-constriction of the spiral arterioles of the myometrium. Reynolds[72] believes that oestrogens are parasympathicomimetic and inhibit choline esterase. Defective oestrogen control of the uterus would therefore encourage the sympathetic vaso-constriction (Hirst, Hamblen and Cuyler[73]). This would account for the successes claimed for oestrogen therapy in about 50 per cent of cases of dysmenorrhoea. Sturgis and Albright[74] believe that dysmenorrhoea takes place only in ovular cycles and that the relief obtained from oestrogens is produced by inhibition of the release of the follicle stimulating hormone of the pituitary, thereby preventing ovulation. To do this it is necessary to commence treatment early in the cycle. They advocate injection of 20,000 I.B.U. of oestradiol benzoate every third day for 6 doses, beginning on the 6th day of the cycle. In 15 premenstrual biopsies preceding painful periods they found a progestational endometrium, whereas 9 biopsies taken immediately before painless periods showed a proliferative endometrium. These findings were not confirmed by Hirst, Hamblen and Cuyler,[73] who observed no relation between the type of bleeding and the presence or absence of dysmenorrhoea.

Good results have also been claimed in cases treated with progestogens. For instance, Soule[75] using 60 mg. of ethisterone daily for 5 or 6 days premenstrually obtained relief in 25 out of 40 cycles, and Greenblatt, McCall and Torpin[76] reported painless periods in 50 per cent of 64 cycles giving 20–240 mg. of ethisterone during the first 3 weeks of the cycle. Elden and Wilson[77] observed improvement in 8 out of 17 cases treated with very low doses of progesterone (2/25 to 1 Rab. U.).

Finally, there have been reports of good results from androgen therapy. Cinberg[78] observed that the pain is most severe during the period of heaviest flow and believes therefore that there is a vascular engorgement of the pelvis which causes the normal luteal contractions to give rise to pain. In the belief that the control of functional uterine bleeding by androgens is due to their reduction of vascular engorgement he gave 10 mg. of testosterone propionate for 3 days before the flow, or 20 mg. of methyl testosterone for 10 days premenstrually, and obtained relief in 14 out of 22 patients.

Geist and Salmon[66] have also reported on the treatment of dysmenorrhoea, giving 250 mg. of testosterone propionate during the course of the cycle: 72 per cent of their cases were relieved.

Whatever may be the mechanism of the painful uterine contractions of dysmenorrhoea there seems little doubt that both oestrogens and androgens are capable of affording relief in about half the cases treated. The role of progesterone in the treatment of dysmenorrhoea does not seem to be so well-established.

THE GONADOTROPHINS AND OVULATION.

The discovery by Aschheim and Zondek,[2] in 1927, of a substance in the urine of pregnant women which could stimulate follicle maturation, ovulation and corpus luteum formation in the ovaries of immature mice, was not only the inauguration of pregnancy diagnosis tests but also the beginning of gonadotrophic therapy. Chorionic gonadotrophin (as it is now termed) was used either in an attempt to stimulate the ovaries of amenorrhoeic women to rhythmical activity or to luteinize the cystic follicles of cases of metropathia haemorrhagica. That this compound by itself has no action on the ovaries of monkeys was shown, however, by Engle,[79] Marshall,[80] Hartman[81] and de Fremery;[82] whereas Campbell,[83] Geist,[84] Hamblen,[85] and Jeffcoate[86] reached similar conclusions in regard to the human ovary. Indeed Brown, Bradbury and Metzger[87] claimed that chorionic gonadotrophic therapy may even lead to amenorrhoea and endometrial atrophy.

In 1930 Cole and Hart[88] isolated from the blood serum of pregnant mares a gonadotrophin which was capable of inducing follicular maturation, ovulation and corpus luteum formation in hypophysectomized animals. This compound apparently is not elaborated by the chorionic villi, for it has been found in the serum of the pregnant mare before placentation has taken place (Davis and Hellbaum[89]). It therefore appears to be a true pituitary secretion. Its extraction from the serum rather than the pituitary of the pregnant mare, however, has the advantage that it is not contaminated by other pituitary trophic hormones, that it can be obtained in much greater quantities, and that its pituitary activity is augmented by haem (which acts non-specifically as, for instance, copper or zinc have been found to act). At the present moment it would appear to be the best available gonadotrophin.

In 1938 Davis and Koff[90] reported that they had succeeded in 16 out of 36 normally menstruating women in inducing ovulation, as shown by the presence of young corpora lutea at laparotomy seventeen hours after the administration intravenously of approximately 500 I.U. of serum gonadotrophin. This was the first time that it had been convincingly claimed that gonadotrophins were capable of affecting the ovaries of the human subject. The results were confirmed the next year by Siegler and Fein,[91] who gave about 300 I.U. intravenously and induced ovulation in 16 out of 30 women. It is to be noted, however, that these results were obtained in normally menstruating women, whose ovaries were therefore presumably adequately sensitive to the gonadotrophic stimulus. Geist, Gaines and Salmon,[92] examined the ovaries of 91 women at operation following injection of various combinations of gonadotrophins. In no case could ovulation be related to therapy. It remained to be seen, however, what effect this gonadotrophin would have on ovaries which were either intrinsically refractory to a normal gonadotrophic stimulus or which by reason of deficient pituitary stimulation had become relatively insensitive. Hartman[93, 94] was able to induce ovulation in only 7 out of 104

experiments on monkeys not ovulating spontaneously, with intravenous doses similar to those used by Davis and Koff.

In the human female with deficient ovarian activity administration of serum gonadotrophin, admittedly not always given intravenously, failed to induce ovulation as judged by endometrial biopsy in the experience, for example, of Hamblen, Cuyler, Wilson and Pullen;[95] Vogt and Sexton;[96] Erving, Sears and Rock[97] and Brewer, Jones and Skiles.[98]

In view of the observations of Davis and Koff[90] it was clear that in serum gonadotrophin there might turn out to be an effective therapeutic weapon in cases where the ovarian failure had given rise to amenorrhoea, oligomenorrhoea or functional bleeding, and many reports began to appear of its effect in cases of this kind. Administration of serum gonadotrophin carries with it, however, certain possible disadvantages. Though it is more purified than true pituitary extracts it is probably inherently protein in nature, and its injection, especially intravenously, is not to be lightly undertaken. It must, of course, unlike the sex steroids, be given by injection for it is quite inactive by mouth. Finally, unlike chorionic gonadotrophin, which because it is derived from human pregnancy urine does not lose its effectiveness after prolonged administration in women, equine serum gonadotrophin induces the development of anti-gonadotrophins when given to human beings (Spence, Scowen and Rowlands[99]), and begins to lose its effect after a course of two to three months. Thus, unless it is capable of permanently restoring ovarian activity in cases of amenorrhoea or functional bleeding, the sex steroids are probably to be preferred. On the whole the effect of serum gonadotrophin is not considered to be markedly superior to sex hormone therapy for these conditions. In fact, Davis and Hellbaum,[89] reviewing gonadotrophic therapy in 1943, state that "pregnant mares' serum is the best available gonadotrophin but its application to gynaecological therapy has been disappointing."

There is, however, one feat which no combination of the sex hormones has yet been able directly to accomplish and that is the induction of ovulation. The occurrence of anovular cycles is of course an absolute bar to fertilization and gonadotrophin therefore presents the only possible means of overcoming this type of sterility. The presence of amenorrhoea, oligomenorrhoea or functional bleeding points to an obvious factor requiring treatment in many cases of sterility. But in addition to such cases there are many (Israel and Mazer[100] put the incidence at 33 per cent of 109 of their series) in which the sterile women give a history of normal and regular cycles. This fact emphasizes the necessity of performing routine endometrial biopsies in the investigation of barren marriages. There is still great reluctance in this country to perform this very simple outpatient procedure.

If, indeed, serum gonadotrophin can induce a subnormally active ovary to ovulate then it is of paramount importance in the treatment of sterility. Despite many reports to the contrary, some of which have already been quoted, there are some workers who have given convincing evidence, based on endometrial biopsy, of ovulation following serum gonadotrophin injection: e.g. Gray[101] (11 out of 43 cases); Kenny and Daley[102] (2 out of 4); Buxton[103] (4 out of 10); Griffith and McBride[104] (7 out of 8). Siegler,[105] giving intramuscular doses of 80 to 160 I.U. with occasional intravenous injections of 240 I.U. on the 14th day of the cycle, reported conception in 11 out of 28 cases of sterility and ovulation in 5 out of 8 anovular cycles, 3 of the patients becoming pregnant.

What they regard as a considerably more promising form of treatment is the "One-Two" cyclic therapy with serum followed by chorionic gonadotrophin of Hamblen, Cuyler, Wilson and Pullen.[95] Whereas only 1 out of 17 cases showed progestational endometrial changes with serum gonadotrophin alone, 17 out of 45 cycles showed progestational endometrial responses, and 51 per cent of 29 patients (suffering from menstrual disorders) showed a clinical response after combined therapy which persisted in the 10 cases followed up. They believe that the clinical effect of this form of treatment is better than with serum gonadotrophin alone but not so satisfactory as "One-Two" oestrogen-progesterone therapy.

The rather striking recent report of Rydberg and Pedersen-Bjergaard[106] on the effects of sequential serum-chorionic gonadotrophic therapy emphasizes that success is probably largely due to dosage. Experimenting with different individual doses and combinations of dosage they found that 5 daily intramuscular injections of 3,000 I.U. of serum gonadotrophin, followed by 1,500 I.U. of chorionic gonadotrophin every other day for 3 doses, is capable of inducing increased urinary oestrogenic output followed by the appearance of pregnanediol excretion and normal menstrual bleeding from a progestational endometrium in cases of long-established secondary amenorrhoea and primary amenorrhoea. This dosage may give rise to intense though temporary ovarian stimulation accompanied by abdominal pain and palpably enlarged ovaries. The enlargement is due to the formation of transient lutein tumours.

Until recently the use of true anterior pituitary gonadotrophic extracts has been disappointing, though de Fremery showed that they produced a follicle-stimulating effect (but no luteinization) in the immature monkey, varying according to the species from which the pituitary extract was derived. Human pituitary extracts gave the most intense reaction of any species studied. Evans, Meyer and Simpson[107] showed however that the pituitary gland contained a factor which augmented the activity of chorionic gonadotrophin. It would appear that serum gonadotrophin, being already a pituitary derivative, is not capable of further augmentation by pituitary extracts. Mazer and Ravetz[108] reported on the effects of a mixture of chorionic gonadotrophin and Evan's pituitary synergist—20 out of 23 women treated pre-operatively with 75–315 "synergy" units showed stimulation of the ovaries. Bleeding was induced in 19 out of 23 amenorrhoeic women, though in only 2 did rhythmic menstruation follow the course of treatment. 2 out of 8 sterile women conceived immediately following a course of 5 injections of 15 synergy units given during the first half of the cycle.

Consideration of the foregoing accounts leaves one with the impression that whereas gonadotrophic therapy to-day does not offer very much in the form of concrete results it certainly holds out the promise of future achievement. Purification, concentration, dosage, timing and suitable combination of the gonadotrophins available, are factors on which much work has still to be done. Eventually there seems every likelihood of this type of treatment playing a most important role in the management of sterility if not of the grosser forms of menstrual disorder.

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BOOK REVIEW

"Atlas of Ovarian Tumours." By GEMMA BARZILAI, M.D. Published by Grune and Stratton, New York, 1943. Pp. 261. Price 10 dollars.

THIS most valuable contribution to the pathology of ovarian tumours consists of a comprehensive description of ovarian tumours combined with some magnificent photomicrographs. At the present day, a contribution of this sort is almost indispensable to all who are interested in ovarian pathology. The photomicrographs are useful for matching and interpreting doubtful sections. All the rare forms of ovarian tumour are illustrated so that the volume can be regarded as comprehensive. The author has obtained his material in Italy, Vienna, Istambul, America, and makes full acknowledgment. As is fashionable in modern work on ovarian tumours, the greatest attention is paid to the rare tumours of doubtful origin. On the other hand, there is a most excellent classification of malignant ovarian tumours, which although unlikely to be universally accepted, is worthy of careful study. The book is designed primarily for pathologists and it is unlikely that the average gynaecologist will find the descriptions of microscopical preparations easy to follow. On the other hand, the descriptions are accurate and for reference purposes the book is unrivalled. Many of the hypotheses which have been suggested to explain the origin of ovarian tumours are debatable but Doctor Barzilai's opinions are put forward with commendable restraint.

WILFRED SHAW

INDEX TO CURRENT LITERATURE

In this Index an endeavour will be made, so far as war conditions permit, to maintain an up-to-date record of all titles bearing on obstetrics and gynaecology and the infant. The classification aims at making immediately available for the reader the titles under the various subject headings. In the majority of instances the title is obtained from the original publication. Where this has been impossible, the title has been obtained from the abstracting journal shown in brackets. Reprints will be welcomed and should be sent to the Editor.

Any inquiries should be addressed to Miss D. F. Atkins, British Postgraduate Medical School, Ducane Road, London, W.12.

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BOOKS

ANATOMY AND PHYSIOLOGY OF THE PELVIS AND REPRODUCTIVE ORGANS

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